Applications for Community Oncology

Nurse Symposium

August 22, 2024

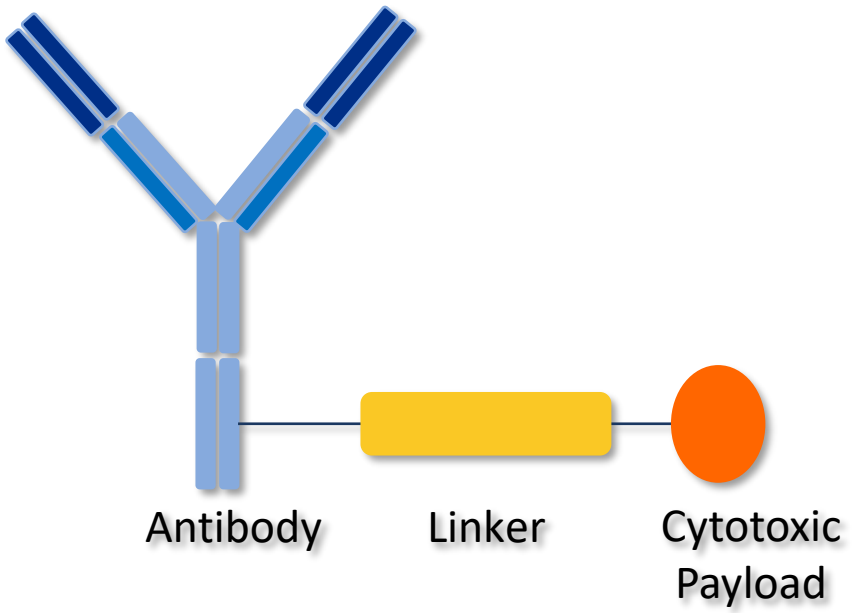
cornerstone specialty network™

Antibody Drug Conjugates

The ABCs of ADCs

Antibody specific targeting delivers the cytotoxic payload or drug to the site of the tumor cells; increased efficacy and reduced systemic exposure and toxicity

Bystander effect occurs where cells within close proximity of the targeted cancer cells are exposed to the antitumor effects of ADCs, irrespective of antigen expression



ADCs consist of a monoclonal antibody linked to a biologically active cytotoxic payload or drug

Cleavage of the linker occurs once internalized in the tumor cell and releases the cytotoxic payload, promoting tumor cell death; drug–antibody ratio (DAR), defined as the number of payload molecules that can be attached to the antibody, influences the potency and therapeutic index of ADCs

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Current FDA Approved Antibody Drug Conjugates (ADCs)

SOLID TUMOR ADCs

- Trastuzumab emtansine (KADCYLA®)
- Trastuzumab deruxtecan (ENHERTU®)
- Enfortumab vedotin (PADCEV®)
- Sacituzumab govitecan (TRODELVY®)
- Mirvetuximab soravtansine-gynx (ELAHERE™)
- Tisotumab vedotin-tftv (TIVDAK)

Breast Cancer

Non-Small Cell Lung Cancer (NSCLC)

Gastric or Gastroesophageal Junction Adenocarcinoma

Urothelial Cancer

FRα positive, platinum-resistant epithelial Ovarian, Fallopian tube, or Primary Peritoneal Cancer

Cervical Cancer

HEMATOLOGICAL ADCs

- Gemtuzumab ozogamicin (MYLOTARG®)
- Brentuximab vedotin (ADCETRIS®)
- Inotuzumab ozogamicin (BESPONSA®)
- Polatuzumab vedotin (POLIVY®)
- Loncastuximab tesirine-lpyl (ZYNLONTA®)

Acute Myeloid Leukemia

classical Hodgkin lymphoma

Anaplastic Large Cell Lymphoma

Diffuse Large B-Cell Lymphoma, not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma

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ADCs: Box Warnings* and Warnings and Precautions

TIVDAK
- **Severe ocular toxicitie***
- Peripheral neuropathy
- Hemorrhage
- Pneumonitis
- Severe Cutaneous Adverse Reactions

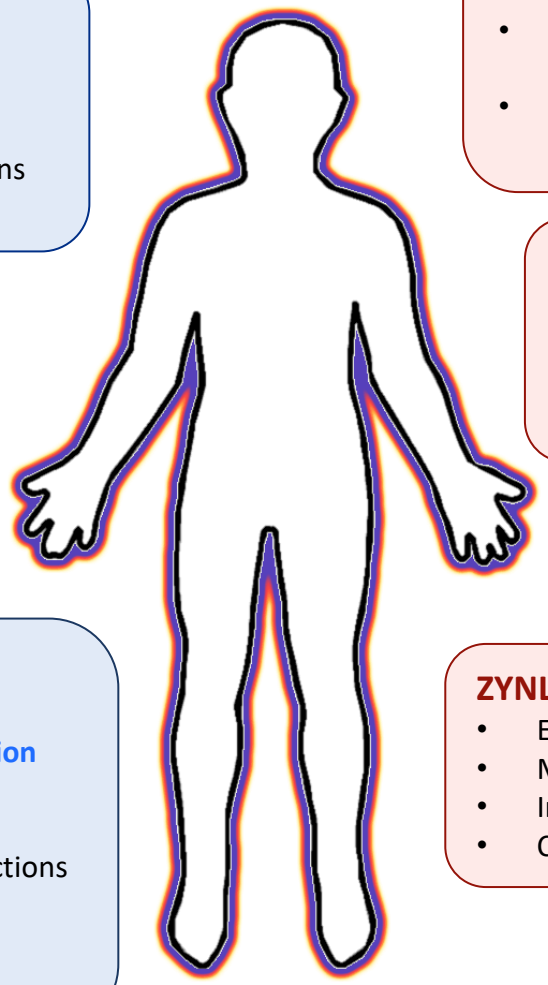
ENHERTU®
- **Interstitial lung disease (ILD) and pneumonitis***
- Neutropenia
- Left ventricular dysfunction

PADCEV®
- **Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)***
- Hyperglycemia
- Pneumonitis/Interstitial Lung Disease (ILD)
- Peripheral Neuropathy
- Ocular Disorders
- Infusion Site Extravasation

TRODELVY®
- **Neutropenia***
- **Diarrhea***
- Hypersensitivity and Infusion-related reactions
- Nausea/Vomiting

ELAHERE™
- **Severe ocular toxicities***
- Pneumonitis
- Peripheral Neuropathy

KADCYLA®
- **Hepatotoxicity***
- **Left ventricular ejection fraction***
- Pulmonary toxicity
- Infusion-Related Reactions
- Hemorrhage
- Thrombocytopenia
- Neurotoxicity



BESPONSA®
- **Hepatotoxicity***
- Myelosuppression
- Infusion related reactions
- QT interval prolongation

MYLOTARG®
- **Hepatotoxicity***
- Infusion related reactions
- Hemorrhage

ZYNLONTA®
- Effusion and Edema
- Myelosuppression
- Infections
- Cutaneous Reactions

ADCETRIS®
- **Progressive multifocal leukoencephalopathy (pml)***
- Peripheral neuropathy
- Anaphylaxis and infusion reactions
- Hematologic toxicities
- Serious infections and opportunistic infections
- Tumor lysis syndrome
- Hepatotoxicity
- Pulmonary toxicity
- Serious dermatologic reactions
- Gastrointestinal complications
- Hyperglycemia

POLIVY®
- Peripheral Neuropathy
- Infusion-Related Reactions
- Myelosuppression
- Serious and Opportunistic Infections
- Progressive Multifocal Leukoencephalopathy (PML)
- Tumor Lysis Syndrome
- Hepatotoxicity

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Key Studies: Antibody Drug Conjugates

ADCs

DESTINY Studies: Fam-trastuzumab DXd

TROPICS Study: Sacituzumab govitecan

Patient Case Study

innovaTV 301: Tisotumab vedotin

TROPION Study: Datopotamab DXd

Patient Case Study

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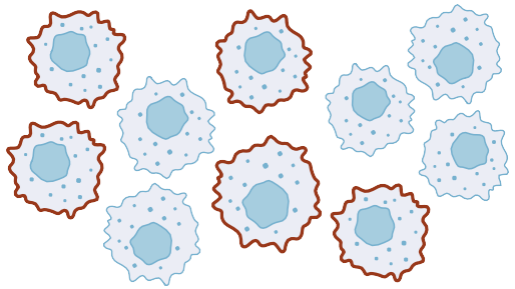
Expanding anti-HER2 strategies to HER2 low and ultralow expressing mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

DESTINY-Breast03 patient population

HER2-positive

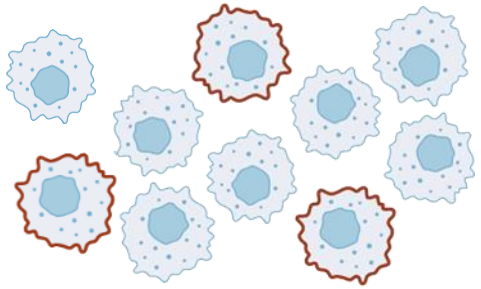


IHC 3+ / IHC2+ ISH+

Membrane staining **complete, intense** and in **>10%** tumor cells

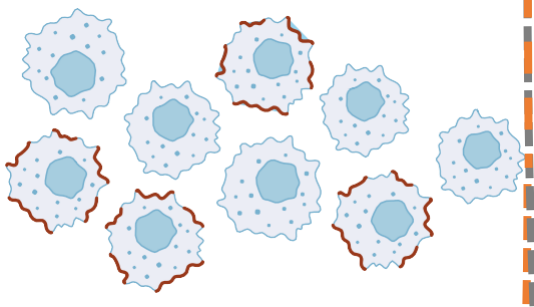
DESTINY-Breast06 patient population: ~85% of HR+, HER2− mBC

HER2-low ~60–65%



IHC 2+

Weak-to-moderate complete membrane staining in **>10%** tumor cells ***OR*** membrane staining is **intense** but **≤10%** tumor cells

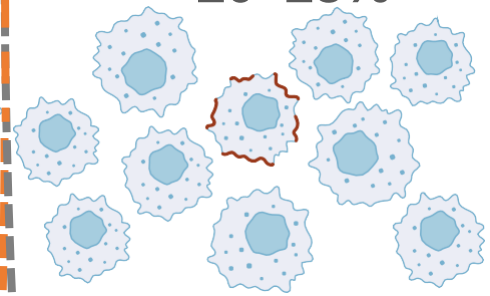


IHC 1+

Faint, **incomplete** membrane staining in **>10%** tumor cells

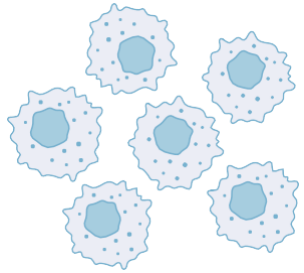
DESTINY-Breast04 patient population: ~60–65% of HR+, HER2− mBC

HER2-ultralow ~20–25%



IHC 0

Faint, incomplete membrane staining in **≤10%** tumor cells



No staining

ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor recep tor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651.

FDA APPROVALS

Fam-trastuzumab deruxtecan-nxki (Enhertu)

*On **January 15, 2021**, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo) for adult patients with locally advanced or metastatic **HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma** who have received a prior trastuzumab-based regimen based on **DESTINY-Gastric01**.*

*On **May 4, 2022**, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic **HER2-positive breast cancer** who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy based on **DESTINY-Breast03**.*

*On **August 5, 2022**, the FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic **HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer** who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on **DESTINY-Breast04**.*

*On **August 11, 2022**, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with **unresectable or metastatic non-small cell lung cancer (NSCLC)** whose tumors have activating **human epidermal growth factor receptor 2 HER2 (ERBB2) mutations**, as detected by an FDA-approved test, and who have received a prior systemic therapy based on **DESTINY-Lung02**.*

*On **April 5, 2024**, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic **HER2-positive (IHC3+) solid tumors** who have received prior systemic treatment and have no satisfactory alternative treatment options based on **DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02.***

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KEY DATA

DESTINY-Breast03

First presented at SABCS 2021

Study Design: Randomized Phase 3 open-label, multicenter study

Stratified by hormone receptor status, prior treatment with pertuzumab, and history of visceral disease

Inclusion Criteria

- Unresectable or metastatic HER2+* (IHC3+ or IHC2+/ISH+) breast cancer
- Previously treated with trastuzumab and taxane in advanced or metastatic setting^
- Could have clinically stable, previously treated brain metastases
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

Randomized 1:1 N=524

T-DXd 5.4 mg/kg q3w n=261

T-DM1 3.6 mg/kg q3w n=263

*HER2 IHC3+ or IHC2+/ISH+ based on central confirmation
^Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

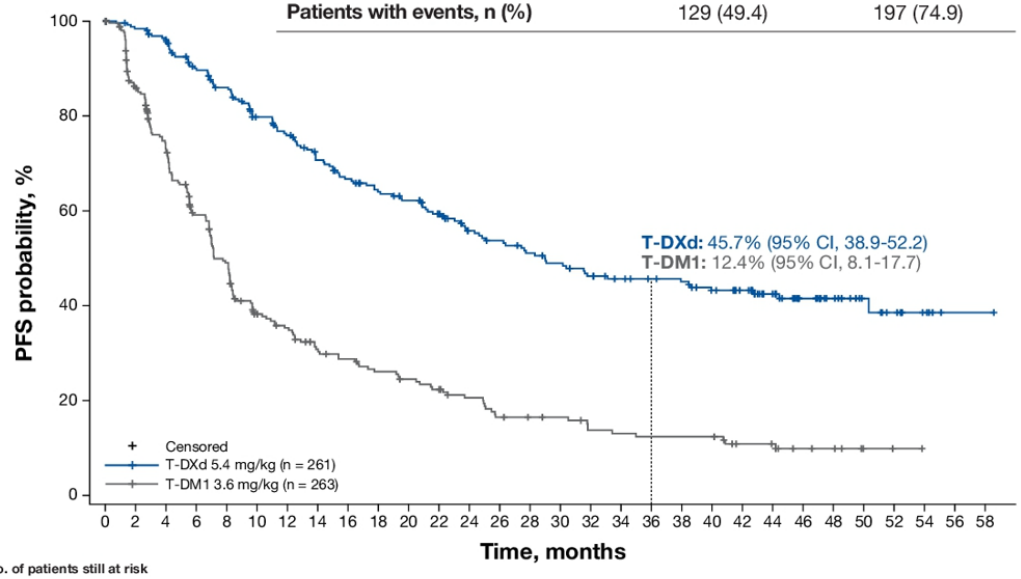
- **Primary End Point:** Progression Free Survival (PFS by Blinded ICR)
- **Secondary Endpoints:** Overall Survival, Overall Response Rate (BIDR and investigator), Duration of Response (BICR), PFS (investigator), safety

T-DXd (Enhertu) versus T-DM1 (Kadcyla): head-to-head study

Updated presented at ASCO 2024

Updated PFS after median duration of follow-up of 41 mo

PFS by investigator Assessment	T-DXd n = 261	T-DM1 n = 263
Median (95% CI), months	29.0 (23.7-40.0)	7.2 (6.8-8.3)
HR (95% CI)	0.30 (0.24-0.38)	
Patients with events, n (%)	129 (49.4)	197 (74.9)



No. of patients still at risk

T-DXd 5.4 mg/kg (n = 261)	261	252	244	222	209	188	177	161	150	141	135	123	107	102	96	91	85	80	77	75	68	62	48	34	23	14	10	5	1	1
T-DM1 3.6 mg/kg (n = 263)	263	216	175	136	111	80	72	60	55	49	45	41	35	28	26	25	20	19	18	18	18	12	11	7	6	2	1	0		

Risk of progression was significantly reduced with T-DXd

Hurvitz. SABCS 2021 (Abstract #GS3-01).

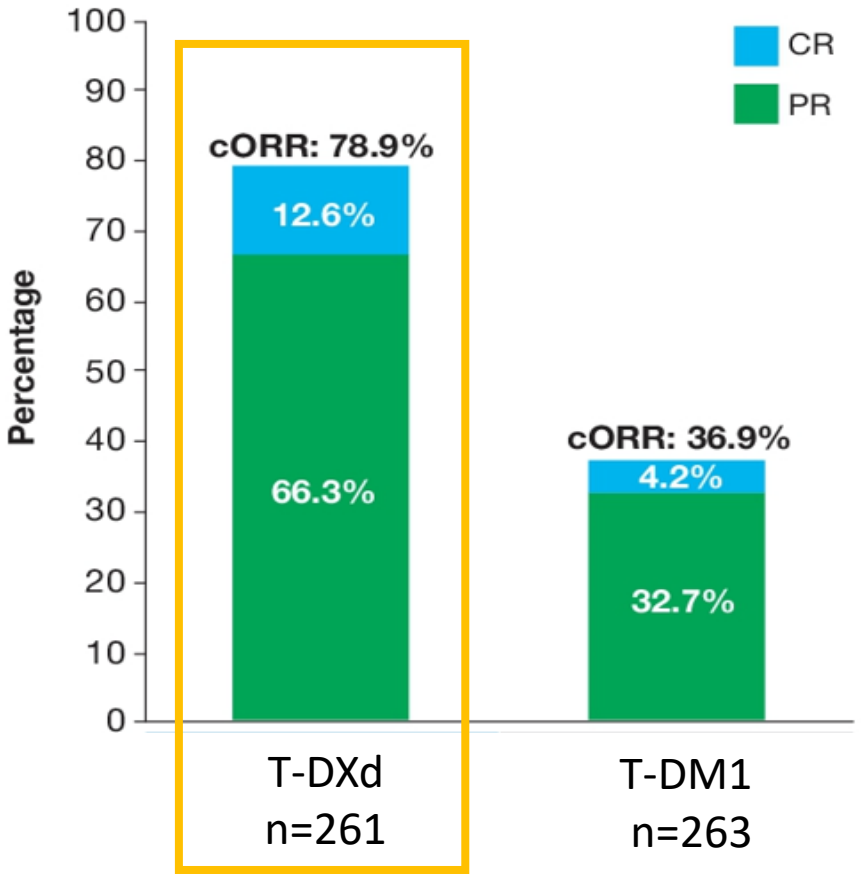
ASCO 2024. Abstr. 1025

KEY DATA

DESTINY-Breast03

Updated presented at ASCO 2024

Updated efficacy and safety, after median duration of follow-up of 41 mo
T-DXd vs T-DM1 in pts with HER2+ mBC treated with ≥1 prior anti-HER2 regimen



ORR: T-DXd more than doubled the response

n (%)	T-DXD n=257	T-DM1 n=261
Any drug related TEAEs	252 (98.1%)	228 (87.4%)
Drug-related grade≥3 TEAEs	125 (48.6%)	111 (42.5%)
Serious drug-related TEAEs	35 (13.6%)	20 (7.7%)
Drug-related TEAEs associated with drug interruption	113 (44.0%)	48 (18.4%)
Drug-related TEAEs associated with dose reduction	72 (28.0%)	40 (15.3%)
Drug-related TEAEs associated with discontinuation	58 (22.6%)	19 (7.3%)
Drug-related TEAEs associated with an outcome of death	0	0

Despite longer treatment duration with T-DXd, safety remains consistent and manageable, with no cumulative toxicities

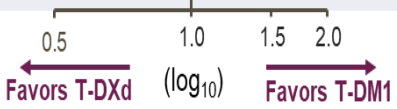
KEY DATA

DESTINY-Breast03: PRO data

First presented at ESMO Breast 2022

- Patient quality of life was assessed using EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L questionnaires

		Median (95% CI) TDD, months		HR (95% CI)	Nominal *P* value
		T-DXd (n = 261)	T-DM1 (n = 263)		
EORTC QLQ-C30	Global health status/QoL[a]	9.7 (7.3-12.5)	8.3 (7.0-10.3)	0.88 (0.70-1.11)	0.2829
	Pain symptoms[b]	10.8 (8.3-14.0)	8.3 (6.6-9.8)	0.75 (0.59-0.95)	0.0146
	Physical functioning[b]	16.7 (14.5-NE)	10.3 (8.3-21.0)	0.77 (0.59-1.01)	0.0529
	Emotional functioning[b]	16.4 (14.1-19.9)	10.5 (9.0-13.8)	0.69 (0.53-0.89)	0.0049
	Social functioning[b]	11.1 (7.3-13.4)	9.0 (7.1-11.3)	0.90 (0.71-1.14)	0.3577
EORTC QLQ-BR45	Arm symptoms[b]	11.1 (8.5-14.8)	7.0 (5.6-9.3)	0.70 (0.55-0.89)	0.0033
	Breast symptoms[b]	26.4 (26.4-NE)	NE (NE-NE)	0.76 (0.53-1.09)	0.1329
EQ-5D-5L	VAS[b]	13.2 (10.1-15.3)	8.5 (7.3-10.4)	0.77 (0.61-0.98)	0.0354



Time to definitive deterioration of quality of life was prolonged in patients receiving T-DXd

- Hospitalization-Related Endpoints

Parameter	T-DXd n = 261	T-DM1 n = 263
Subjects with hospitalization, n (%)	18 (6.9)	19 (7.2)
Median (range) time to first hospitalization[a], days	219.5 (0-723)	60.0 (0-399)
Median (range) length of hospital stay, days	10.5 (1-181)	9.0 (2-25)
Died, n (%)	2 (0.8)	1 (0.4)
Discharged home, n (%)	15 (5.7)	16 (6.1)
Discharged to home health care, n (%)	1 (0.4)	1 (0.4)

Median time to hospitalization was more than 3 times longer in the T-DXd arm vs T-DM1 arm

ESMO Breast 2022 Abstr 1630

KEY DATA

DESTINY-Breast04

First presented at ASCO 2022

Study Design: Multicenter, randomized, open-label phase III trial

Stratified by HER2-low status (IHC1+ vs IHC2+ and ISH-), # of prior lines of chemotherapy (1 vs 2), HR status (HR+ [with vs without previous CDK4/6 inhibitor] vs HR-)

- HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable or metastatic breast cancer
- 1-2 lines of chemotherapy in the metastatic setting or recurrence ≤6 mo after adjuvant CT
- ≥1 ET if HR+ (~90% of pts)
- Treated, stable brain metastases eligible

(N = 557)

R 2:1

T-DXd 5.4 mg/kg q3w (n = 373)

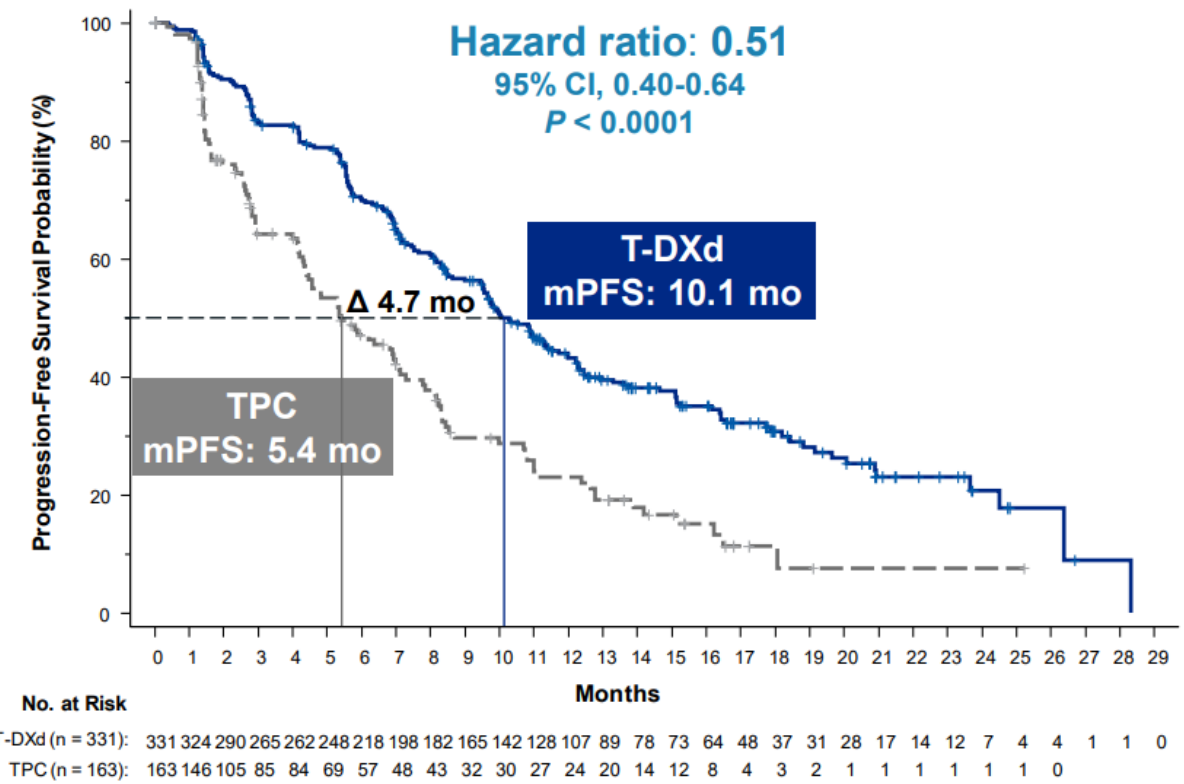
Treatment of physician's choice (TPC) (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) (n = 184)

Data cutoff: January 11, 2022

Primary endpoints: PFS by BICR (HR+)
Key secondary endpoints: PFS by BICR (all patients); OS (HR+ and all patients)

T-DXd is the first HER2-targeted therapy to demonstrate benefit to patients with HER2-low advanced breast cancer

PFS was almost doubled with T-DXd



Risk of progression was significantly reduced with T-DXd

ASCO 2022. Abstr LBA03.

DESTINY-Breast04

Overall Safety

n (%)	Safety analysis set[a]	
	T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years[b]	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

T-DXd: safety remains consistent and manageable

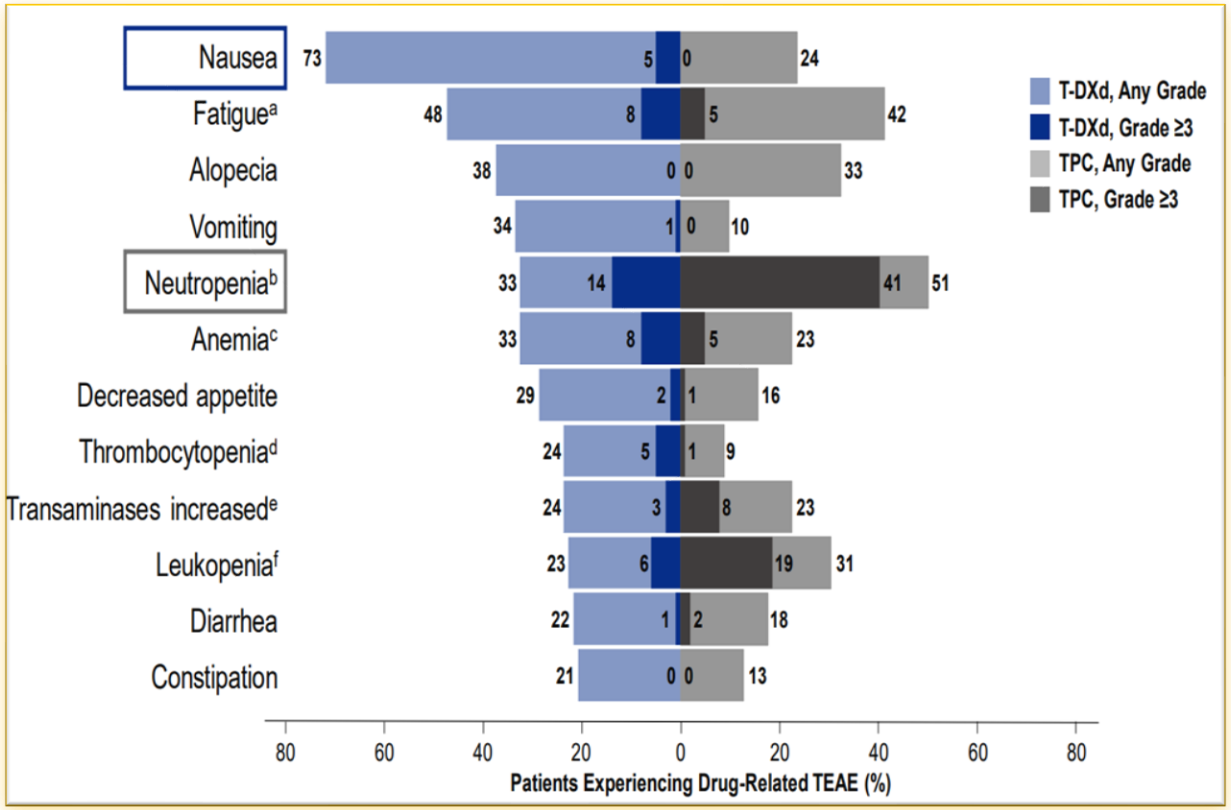
- **Median treatment duration**
  - **T-DXd: 8.2 months** (range: 0.2 – 33.3)
  - **TPC: 3.5 months** (range: 0.3 – 17.6)
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - **T-DXd: 4.6%, nausea and fatigue[d]**
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [c]Grouped term. [d]Fatigue includes the preferred terms fatigue, malaise, and asthenia; neutropenia included the preferred terms of neutropenia and neutrophil count decreased. [e]On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug irrespective of the cause; the TEAEs associated with deaths represent a subset of on-treatment deaths reported by the investigators as adverse events.

ASCO 2022. Abstr LBA03.

DESTINY-Breast04

Drug-Related TEAEs in ≥20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Nausea: mostly Grade 1 or 2

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to recovered.

Monitoring and management of ILD remains important

KEY DATA

DESTINY-Breast06

T-DXd is the first HER2-targeted therapy to demonstrate benefit to patients with HER2-ultralow advanced breast cancer

First presented at ASCO 2024

Study Design: randomized, multicenter, open-label Phase 3 study

Stratified by Prior CDK4/6i use (yes vs no); HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining); Prior taxane in the non-metastatic setting (yes vs no)

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)
- **Chemotherapy naïve in the mBC setting**
- Prior lines of therapy
  - ≥2 lines of ET ± targeted therapy for mBC OR
  - 1 line for mBC AND
    - Progression ≤6 months of starting first-line ET + CDK4/6i OR
    - Recurrence ≤24 months of starting adjuvant ET

(HER2-Low = 713; HER2-ultralow = 153)

R 1:1

T-DXd
5.4 mg/kg q3w
(n=436)

(HER2-Low: n= 713; HER2-ultralow: n= 153)

TPC
Options: capecitabine, nab-paclitaxel, paclitaxel
(n=430)

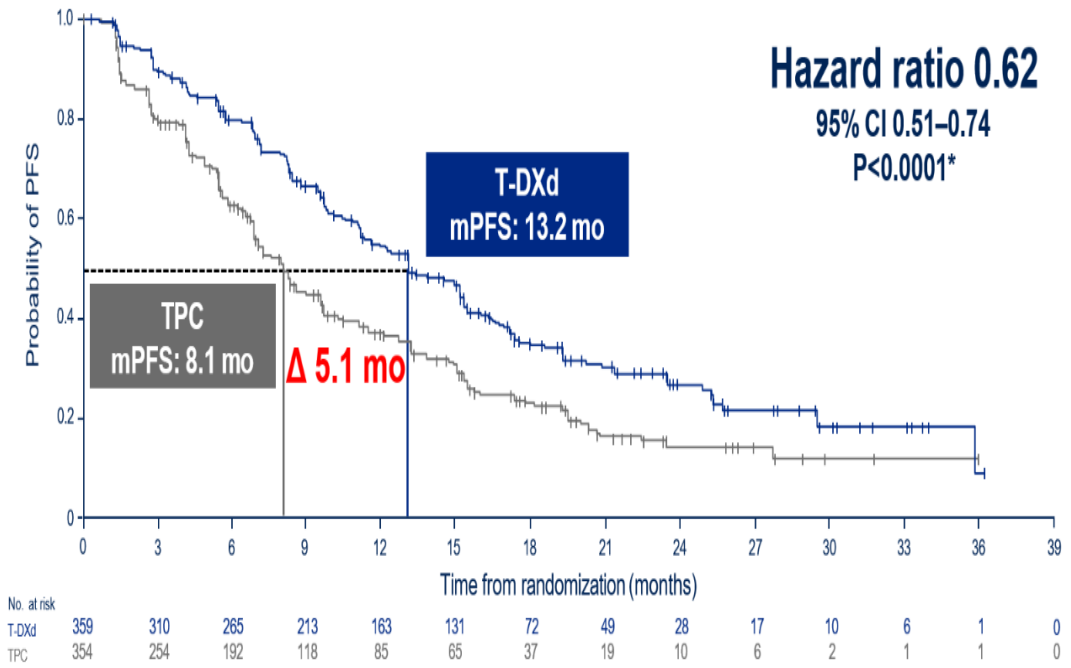
Primary endpoint:
- PFS (BICR) in HER2-low

Key secondary endpoints:
- PFS (BICR) in ITT (HER2-low + ultralow), OS in HER2-low, OS in ITT (HER2-low + ultralow)

Other Endpoints:
- PFS (INV) in HER2-low, ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow), Safety and tolerability, Patient-reported outcomes‡

Data Cut Off: March 18, 2024

Primary Endpoint: PFS (BICR) in HER2-low

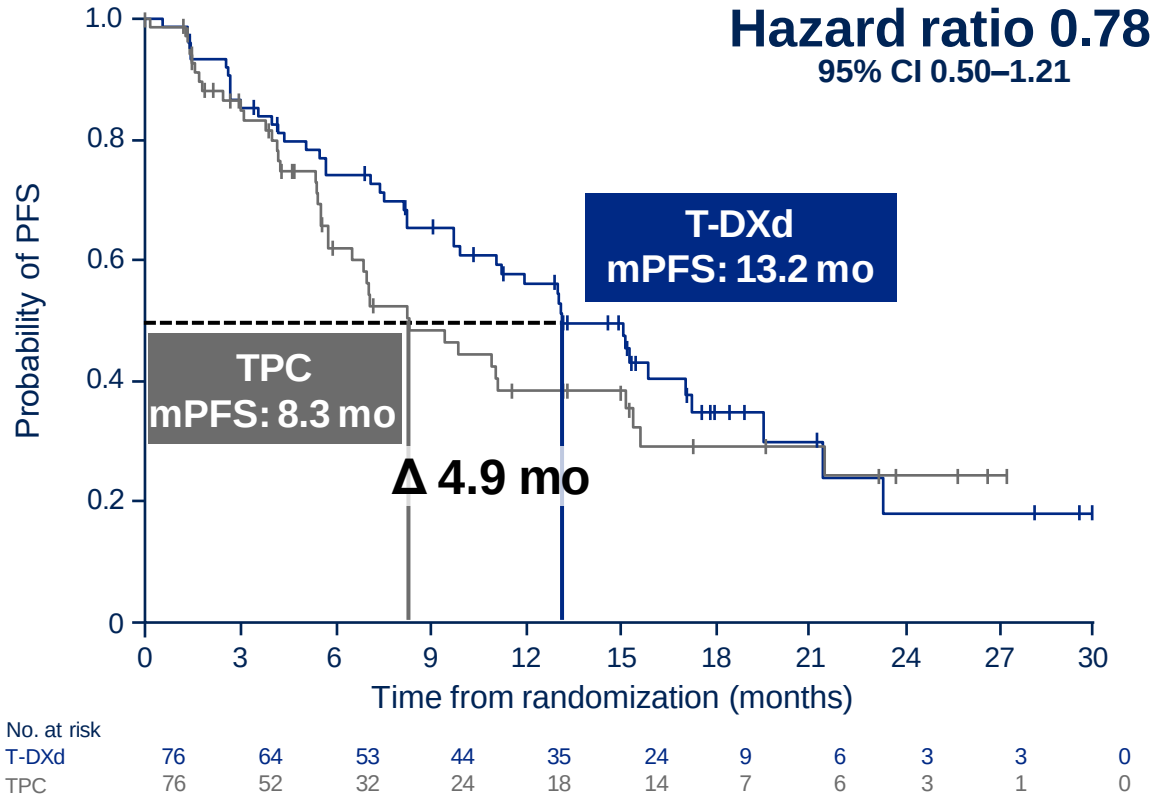


Risk of progression was significantly reduced in HER2-low with T-DXd

KEY DATA

DESTINY-Breast06

Exploratory Endpoint: PFS in *HER2-ultralow*



*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overal l survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Data Cut Off: March 18, 2024

	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	**203 (56.5)**	**114 (32.2)**	**250 (57.3)**	**134 (31.2)**	**47 (61.8)**	**20 (26.3)**
Best overall response, n (%)						
Complete response	**9 (2.5)**	0	**13 (3.0)**	0	**4 (5.3)**	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median duration of response, mo	14.1	8.6	14.3	8.6	14.3	14.1

Risk of progression was reduced with T-DXd in HER2-ultralow

ORR: T-DXd almost doubled the response across all groups

ASCO 2024. Abstr LBA 1000

KEY DATA

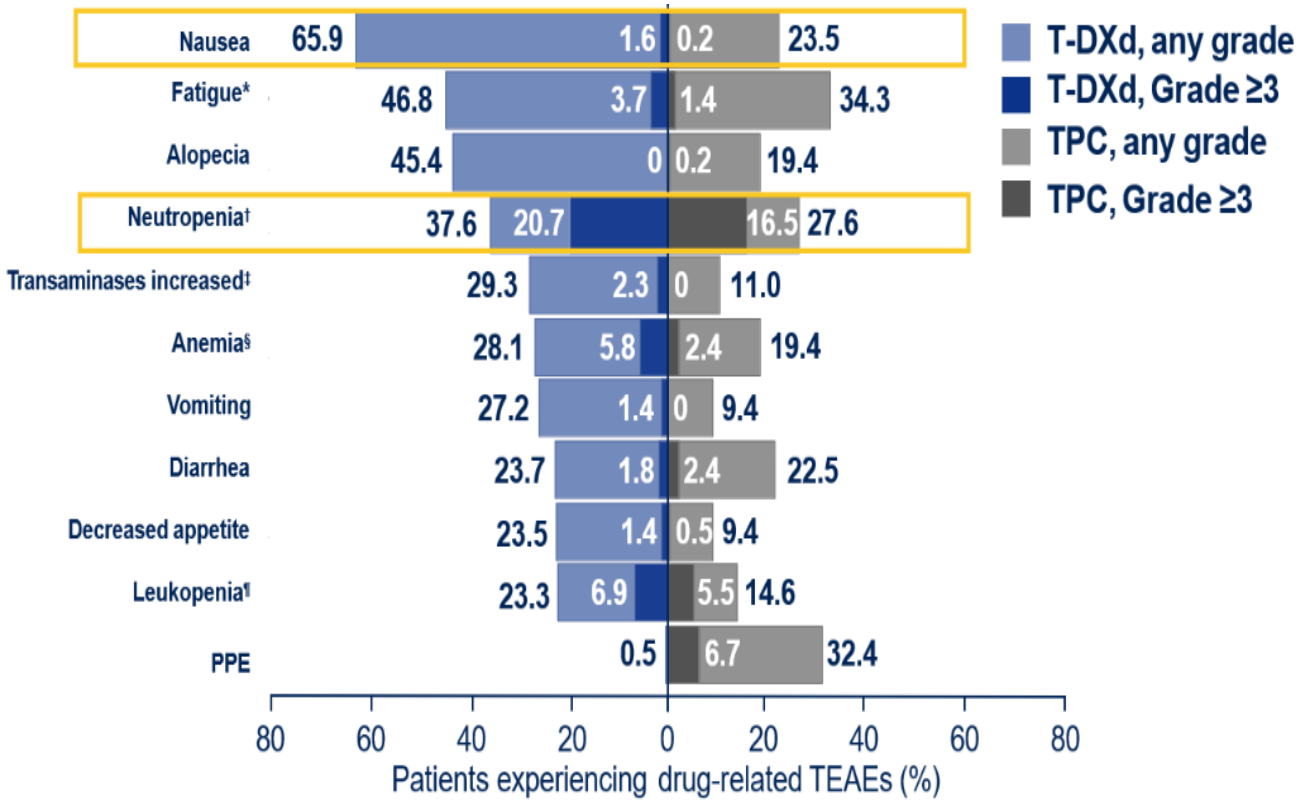
DESTINY-Breast06

Safety Summary

	T-DXd (n=434)	TPC (n=417)
Total exposure, patient-years	438.5	263.5
Any TEAE, n (%)	429 (98.8)	397 (95.2)
Treatment-related TEAEs, n (%)	417 (96.1)	373 (89.4)
Grade ≥3	176 (40.6)	131 (31.4)
Serious TEAEs, n (%)	88 (20.3)	67 (16.1)
TEAEs associated with treatment discontinuation, n (%)	62 (14.3)	39 (9.4)
TEAEs associated with dose interruptions, n (%)	210 (48.4)	160 (38.4)
TEAEs associated with dose reductions, n (%)	107 (24.7)	161 (38.6)
TEAEs leading to death, n (%)	11 (2.5)	6 (1.4)
Treatment related (investigator assessed)	5 (1.2)	0

- **Median treatment duration:**
  - **T-DXd: 11.0 mo (range 0.4–39.6) vs TPC: 5.6 mo (range 0.1–35.9)**
- Most common TEAE associated with treatment discontinuation:
  - T-DXd: 5.3%, pneumonitis vs TPC: 1.4%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction:
  - **T-DXd: 4.4%, nausea** vs TPC: 16.5%, PPE

Drug-related TEAEs in ≥20% of patients (either treatment group)



T-DXd: safety remains consistent and manageable

ASCO 2024. Abstr LBA 1000

KEY DATA

DESTINY-PanTumor02

First presented at ASCO 2023

Study Design: Open-label, multicenter, Phase II study

- Patients with **advanced solid tumor** not eligible for curative therapy
- 2L + patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines)*
- Prior HER2-targeting therapy allowed
- ECOG / WHO PS 0-1

*All patients centrally confirmed

T-DXd 5.4 mg/kg q3w

n≈40 per cohort planned

Cohorts with no objective responses in the first 15 patents were to be closed

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Billary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors

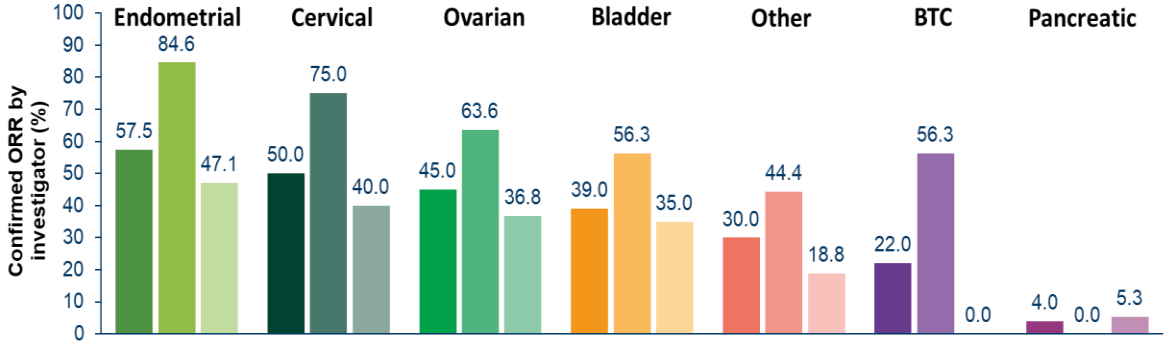
Primary endpoints: Confirmed ORR (investigator)
Secondary endpoints: DOR, DCR, PFS, OS, Safety
Exploratory endpoint: Subgroup analyses by HER2 status

[a] Patients were eligible for either test. All patients were centrally confirmed. [b] Cohorts with no objective responses in the first 15 patients were to be closed. [c] Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non–small cell lung cancer, gastric cancer, and colorectal cancer. [d] Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

1. Meric-Bernstam F, et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid, Spain. LBA34. 2. Meric-Bernstam F, et al. *J Clin Oncol.* October 2023. Online ahead of print. doi:10.1200/JCO.23.02005
3. Hofmann M, et al. *Histopathology.* 2008;52(7):797-805.

Data cutoff : June 8, 2023

ORR and DoR by HER2 Status



Median DoR, months (95% CI)[b]	NR (9.9-NR)	14.2 (4.1-NR)	11.3 (4.1-22.1)	8.7 (4.3-11.8)	22.1 (4.1-NR)	8.6 (2.1-NR)	5.7 (NR-NR)

	All patients (N =267)	IHC 3+ (n =75)	IHC 2+ (n =125)
ORR, % (95% CI)	37.1 (31.3-43.2)	61.3 (49.4-72.4)	27.2 (19.6-35.9)
Median DoR, months (95% CI)[b]	11.3 (9.6-17.8)	22.1 (9.6-NR)	9.8 (4.3-12.6)

Analysis of ORR by investigator was performed in patients who received ≥ 1 dose of T-DXd; all patients (N = 267; including 67 patients with IHC 1+ [n = 25], IHC 0 [n = 30], or unknown IHC status [n = 12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n = 75) or IHC 2+ (n = 125) status. Analysis of DoR was performed in patients with objective response who received ≥ 1 dose of T-DXd; all patients (n = 99; including 19 patients with IHC 1+ [n = 6], IHC 0
[n = 9], or unknown IHC status [n = 4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n = 46) or IHC 2+ (n = 34) status.
[a] Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer. [b] Includes patients with a confirmed objective response only.

1. Meric-Bernstam F, et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid, Spain. LBA34. 2. Meric-Bernstam F, et al. *J Clin Oncol.* 2023. doi:10.1200/JCO.23.02005

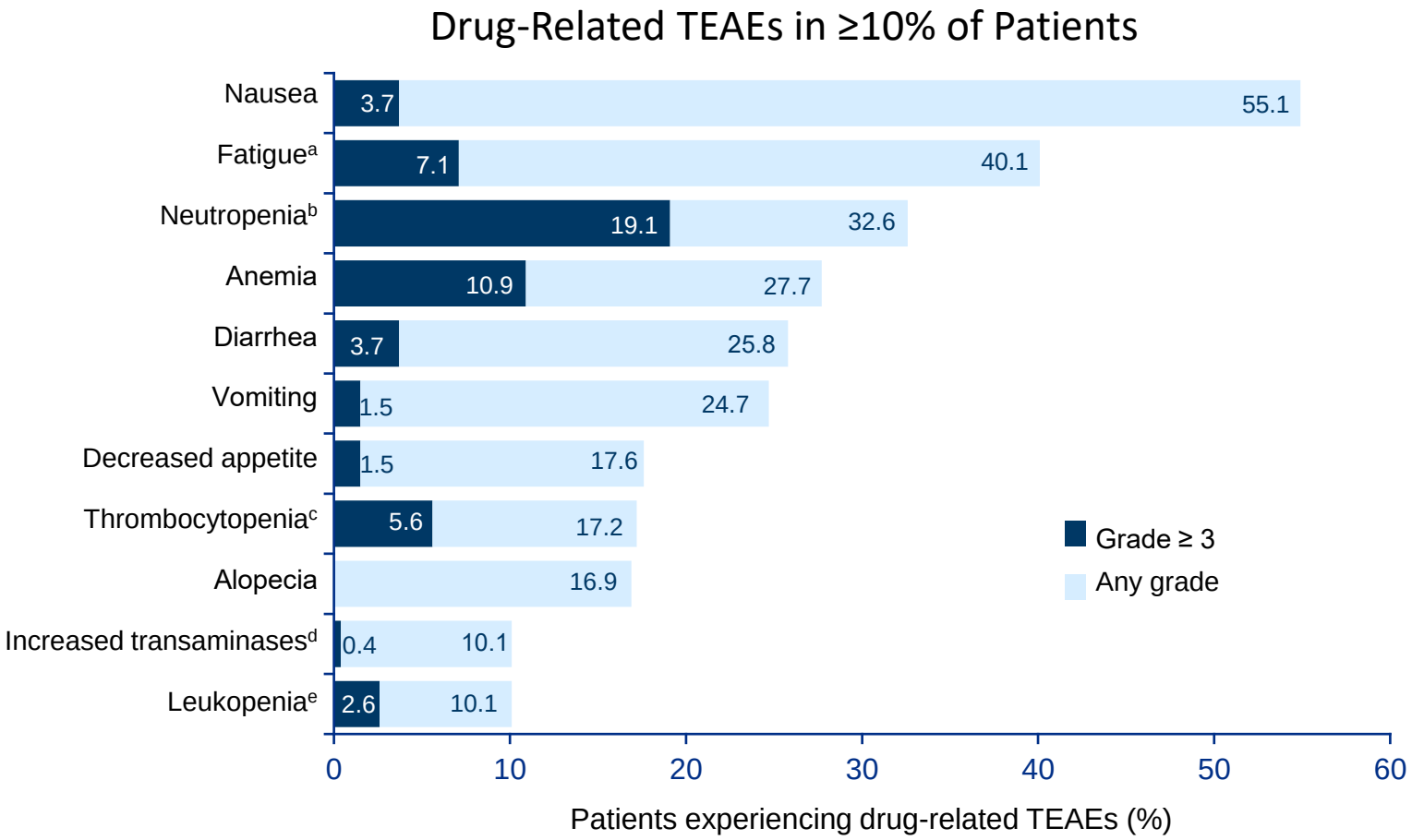
T-DXd: activity across all tumor types investigated
Greatest benefit for tumors with IHC 3+ status

DESTINY-PanTumor02

Safety

n (%)	All patients (N=267)
Any drug-related TEAs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with death	4 (1.5)*

Analyses included patients who received ≥ 1 dose of T-DXd (N = 267); median total treatment duration 5.6 months (range, 0.4-31.1).
[a] Category includes the preferred terms fatigue, asthenia, and malaise. [b] Category includes the preferred terms neutrophil count decreased and neutropenia. [c] Category includes the preferred terms platelet count decreased and thrombocytopenia. [d] Category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia. [e] Category includes the preferred terms white blood cell count decreased and leukopenia.
Meric-Bernstam, et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid, Spain. LBA34.



Nausea remains greatest side effect; management important to stay on treatment

Key Studies: Antibody Drug Conjugates

ADCs

DESTINY Studies: Fam-trastuzumab DXd

TROPICS Study: Sacituzumab govitecan

Patient Case Study

innovaTV 301: Tisotumab vedotin

TROPION Study: Datopotamab DXd

Patient Case Study

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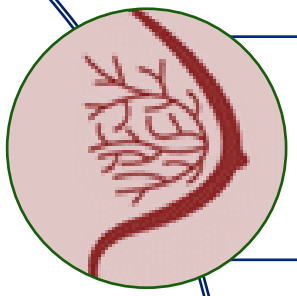
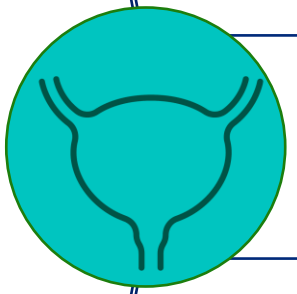
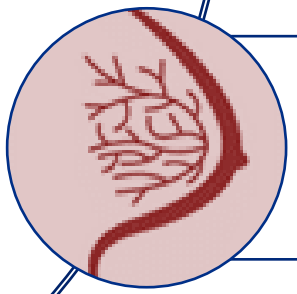
Sacituzumab govitecan (Trodelvy)



*On **April 7, 2021**, the FDA granted regular approval to sacituzumab govitecan (Trodelvy, Immunomedics Inc.) for patients with unresectable locally advanced or **metastatic triple-negative breast cancer (mTNBC)** who have received two or more prior systemic therapies, at least one of them for metastatic disease (Previously received accelerated approval April 2020) based on the **ASCENT** trial.*



*On **April 13, 2021**.the FDA has granted accelerated approval of Trodelvy (sacituzumab govitecan-hziy) for use in adult patients with **locally advanced or metastatic urothelial cancer (UC)** who have previously received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor based on the **TROPHY** trial.*



*On **February 3, 2023**, the FDA approved sacituzumab govitecan-hziy (Trodelvy, Gilead Sciences, Inc.) for patients with unresectable **locally advanced or metastatic hormone receptor (HR)-positive HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer** who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting based on **TROPICS-02** trial.*

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KEY DATA

TROPiCS-02

First presented at ASCO 2022

Study Design: Randomized, multicenter, open-label phase III study

Stratification by visceral metastases (yes vs no), ET in metastatic setting ≥6 mo (yes vs no), prior lines of chemotherapy (2 vs 3/4)

- Metastatic or locally recurrent, inoperable HR+/HER2- breast cancer with disease progression
- At least 1 ET, taxane, and CDK4/6 inhibitor in any setting
- 2-4 previous lines of CT for metastatic disease (neo/adjuvant therapy qualified as a prior line of CT if disease recurred within 12 mo)
- Measurable disease by RECIST v1.1

(N = 543)

R 1:1

Sacituzumab Govitecan
10 mg/kg IV Days 1 and 8, every 21 days
(n = 272)

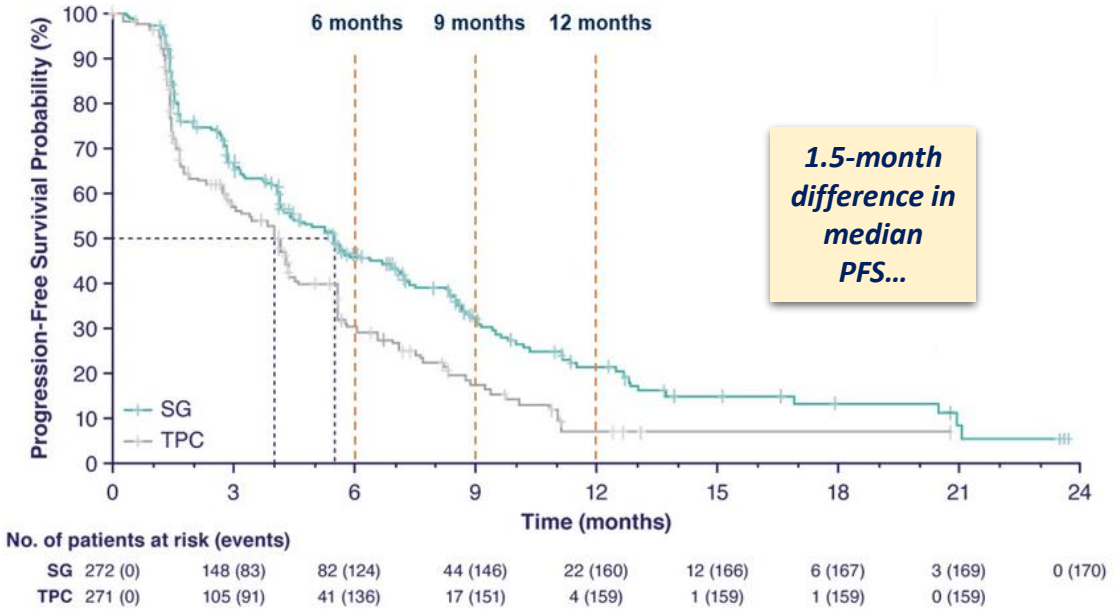
Until PD or unacceptable toxicity

Physician's Choice of Treatment*
(*Capecitabine, vinorelbine, gemcitabine, or eribulin)
(n = 271)

Primary endpoint: PFS (BICR)
Secondary endpoints: OS, ORR, DoR, CBR (by LIR and BICR), PRO, safety

Classically defined HR+/HER2-negative; heavily pretreated

PFS in the ITT Population



1.5-month difference in median PFS…

BICR Analysis	Sacituzumab Govitecan (n = 272)	Physician's Choice (n = 271)
Median PFS, mo (95% CI)	**5.5 (4.2-7.0)**	**4.0 (3.1-4.4)**
• Stratified hazard ratio (95% CI)	**0.66 (0.53-0.83)**	
• Stratified log-rank *P* value	**0.0003**	
6-mo PFS, % (95% CI)	46.1 (39.4-52.6)	30.3 (23.6-37.3)
9-mo PFS, % (95% CI)	32.5 (25.9-39.2)	17.3 (11.5-24.2)
12-mo PFS, % (95% CI)	21.3 (15.2-28.1)	7.1 (2.8-13.9)

Statistically significant but modest clinical benefit

ASCO 2022. Abstr LBA1001.

KEY DATA

TROPiCS-02

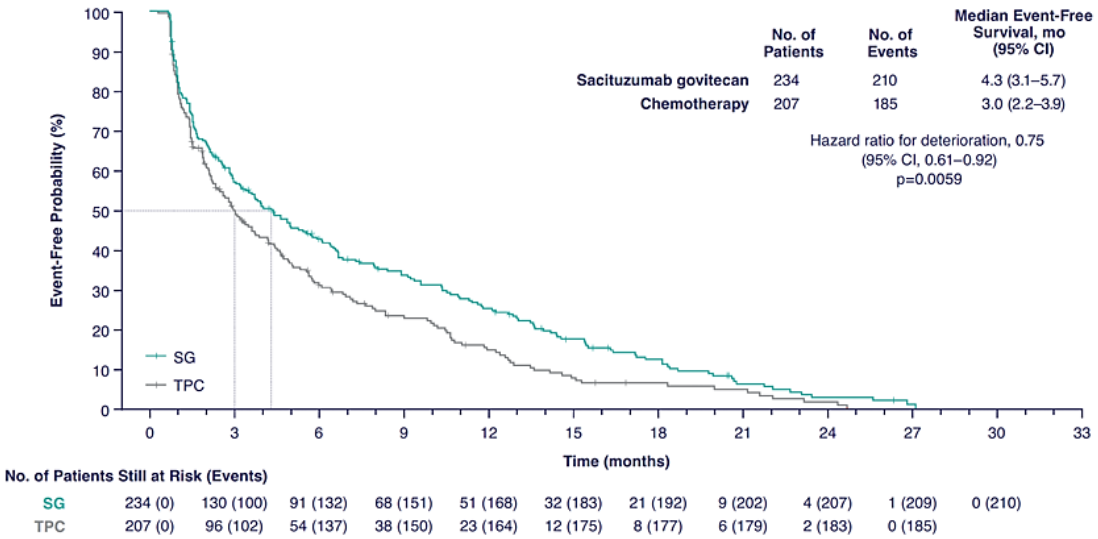
Safety: Treatment-related AEs – All Grade and Grade ≥3

TRAEs, n (%)	Sacituzumab Govitecan (n = 268)		Physician's Choice (n = 249)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic				
• Neutropenia	188 (70)	**136 (51)**	134 (54)	94 (38)
• Anemia	91 (34)	**17 (6)**	62 (25)	8 (3)
• Leukopenia	37 (14)	**23 (9)**	23 (9)	13 (5)
• Lymphopenia	31 (12)	**10 (4)**	25 (10)	8 (3)
• Febrile neutropenia	14 (5)	**14 (5)**	11 (4)	11 (4)
Gastrointestinal				
• Diarrhea	152 (57)	**25 (9)**	41 (16)	3 (1)
• Nausea	148 (55)	3 (1)	77 (31)	7 (3)
• Vomiting	50 (19)	1 (<1)	30 (12)	4 (2)
• Constipation	49 (18)	0	36 (14)	0
• Abdominal pain	34 (13)	2 (1)	17 (7)	0
Other				
• Alopecia	123 (46)	0	41 (16)	0
• Fatigue	100 (37)	15 (6)	73 (29)	6 (2)
• Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
• Decreased appetite	41 (15)	1 (<1)	34 (14)	1 (<1)
• Neuropathy	23 (9)	3 (1)	38 (15)	6 (2)

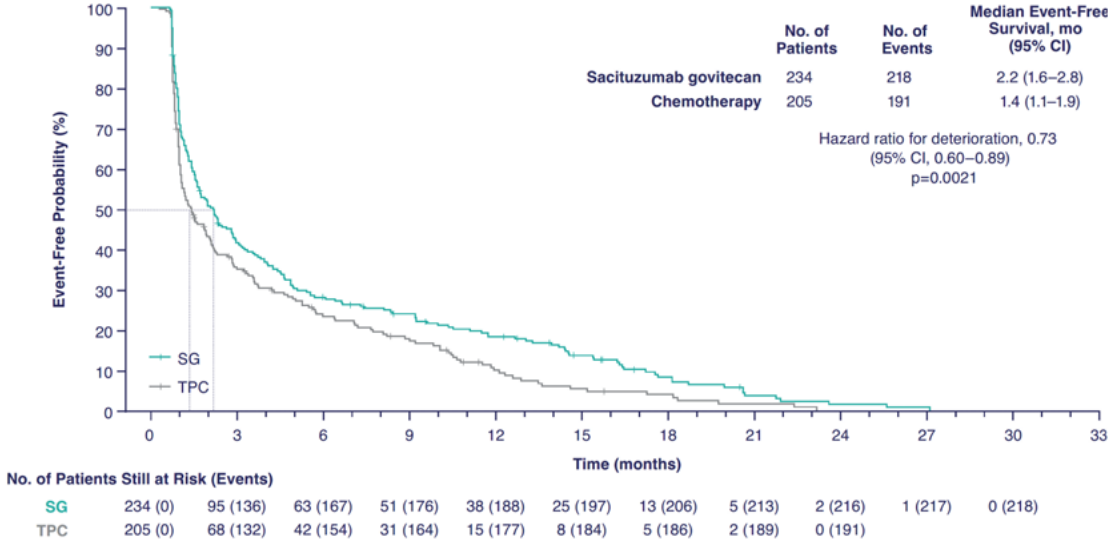
Note: No ILD events in the SG arm vs 1% in the TPC arm; no TRAEs of cardiac failure or LV dysfunction in either arm

GI and hematologic toxicities noted

Estimates of Time to Deterioration of Global Health Status/QoL Scale



Estimates of Time to Deterioration of Fatigue Scale



ASCO 2022. Abstr LBA1001.

Patient Case Study

Katie Alexander

HER2-low Breast Cancer

Active 63-year-old, enjoys pickle ball, traveling, and spending time with her family

Diagnostic information: ER positive breast cancer (2007): ER+, PR+, HER2 2+, FISH nonamplified

1st line treatment

s/p bilateral mastectomies and adjuvant chemo with TC (2007)

2nd line treatment

Recurrent metastatic disease (12/2018)

Started palbociclib with anastrozole (1/2019)

c/b neutropenia and thrombocytopenia.

Improved tolerance with dose reduction of Ibrance to 75mg.

3rd line treatment

Progressive disease with malignant ascites (4/2021).

Transitioned to Faslodex/Piqray based on Guardant 360 results showing PIKD3CA mutation.

Course complicated by nausea, hospitalizations, hyperglycemia and DKA. Discontinued.

4th line treatment

Progressive disease with new liver lesions.

Transitioned to chemotherapy with Abraxane (6/2021)

Stable disease control on Abraxane with symptom management. Imaging and CA 15-3 stable to improved. Intermittent chemo holidays due to patient requests and travel plans.

Developed intolerance of Abraxane (neuropathy, vision changes)

What next?

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HER2-low Breast Cancer

Active 63-year-old, enjoys pickle ball, traveling, and spending time with her family

Diagnostic information: ER positive breast cancer (2007): ER+, PR+, HER2 2+, FISH nonamplified

*On **August 5, 2022**, the Food and Drug Administration approved **fam-trastuzumab deruxtecan-nxki (Enhertu)** for adult patients with unresectable or metastatic **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on **DESTINY-Breast04***

Diagnostics

6/2022: Reviewed initial pathology, patient with Her2 2+ disease indicating possible role for Enhertu

Enhertu ordered as next line of therapy in light of HER2 2+ (low) and PFTs completed in 9/2022 in light of possible preparation given AE of possible associated ILD

5th line treatment

Enhertu approved, initiated on 11/16/22

Tolerating well overall, small right pleural effusion which was monitored

But course eventually complicated by nausea and erythroderma

What is the best management strategy to stay on therapy?

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NCCN Guidelines Version 1.2024 Antiemesis

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EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[a]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4 • Carmustine >250 mg/m²	• Cisplatin • Cyclophosphamide >1500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m² • Epirubicin >90 mg/m² • Fam-trastuzumab deruxtecan-nxki	• Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Melphalan ≥140 mg/m² • Sacituzumab govitecan-hziy • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[a]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Bendamustine • Busulfan • Carboplatin[b] AUC <4 • Carmustine[b] ≤250 mg/m² • Clofarabine • Cyclophosphamide[b] ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[b] • Daunorubicin[b]	• Dinutuximab • Doxorubicin[b] <60 mg/m² • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Epirubicin[b] ≤90 mg/m² • Idarubicin[b] • Ifosfamide[b] <2 g/m² per dose • Irinotecan[b] • Irinotecan (liposomal) • Lurbinectedin	• Melphalan <140 mg/m² • Methotrexate[b] ≥250 mg/m² • Mirvetuximab soravtansine-gynx • Naxitamab-gqgk • Oxaliplatin[b] • Romidepsin • Temozolomide • Trabectedin[b]

Table framework is based on the emetogenicity classifications described in the following publications: Hesketh PJ, et al. J Clin Oncol 1997;15:103-109. Grunberg SM, et al. Support Care Cancer 2011;19:S43-S47.

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Chemotherapy-induced nausea and vomiting can be classified into four subtypes:

1. ***Acute*** *CINV occurs within 24 hours of receiving chemotherapy*
2. ***Delayed*** *CINV occurs most frequently 24 to 48 hours after chemotherapy but can occur up to 5 days post chemotherapy*
3. ***Anticipatory*** *CINV can occur hours to days before a patient receives chemotherapy*
4. ***Refractory*** *CINV can occur at any point in a treatment cycle, despite adequate therapy for acute and delayed CINV*

- ***What is your preferred high antiemetic risk regimen?***
- ***Prophylactic or reactive?***
- ***Does your choice of high antiemetic risk regimen differ between agents? Between tumor types?***

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NCCN Guidelines Version 1.2024 Antiemesis

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HIGH EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION[f,g,h,i,j]

DAY 1: Select treatment option A, B, or C All treatment options are category 1 and should be started before anticancer therapy[h]	DAYS 2, 3, 4:
Treatment option A (preferred), use the following combination[k]: 1. Olanzapine 5–10 mg PO once[l] 2. NK1 receptor antagonist (RA) (choose one): ◊ Aprepitant 125 mg PO once ◊ Aprepitant injectable emulsion 130 mg intravenous (IV) once[m] ◊ Fosaprepitant 150 mg IV once ◊ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once ◊ Rolapitant 180 mg PO once[n] 3. 5-HT3 RA (choose one)[o,p]: ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg subcutaneous (SQ) once,[q] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ◊ Palonosetron 0.25 mg IV once 4. Dexamethasone 12 mg PO/IV once[r,s]	**Treatment option A:** • Olanzapine 5–10 mg PO daily on days 2, 3, 4[l] • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO is used on day 1) • Dexamethasone 8 mg[r,s] PO/IV daily on days 2, 3, 4
Treatment option B, use the following combination: 1. Olanzapine 5–10 mg PO once[l] 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg PO/IV once[r,s]	**Treatment option B:** • Olanzapine 5–10 mg PO daily on days 2, 3, 4[l]
Treatment option C, use the following combination: 1. NK1 RA (choose one): ◊ Aprepitant 125 mg PO once ◊ Aprepitant injectable emulsion 130 mg IV once[m] ◊ Fosaprepitant 150 mg IV once ◊ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once ◊ Rolapitant 180 mg PO once[n] 2. 5-HT3 RA (choose one)[o,p]: ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg SQ once,[q] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ◊ Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg PO/IV once[r,s]	**Treatment option C:** • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO is used on day 1) • Dexamethasone 8 mg[r,s] PO/IV daily on days 2, 3, 4

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Footnotes on AE-5A

NCCN Guidelines provides antiemesis recommendations for high emetic risk anticancer agents

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*Bucket strategy for managing CINV with high emetic risk: Pick only one drug from each bucket**

3-drug regimen

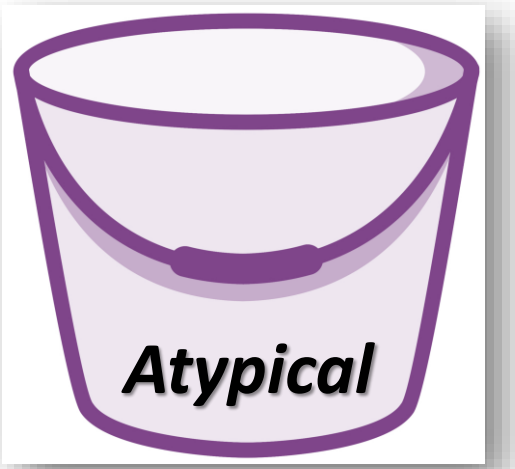
Aprepitant
Rolapitant
Fosaprepitant
Netupitant

Dolasetron
Granisetron
Ondansetron
Palonosetron

Dexamethasone

Additional option

Olanzapine*



2-drug regimen

**Based on NCCN Guidelines*

*Olanzapine is an atypical antipsychotic agent of the thiobenzodiazepine class that has the ability to block many different receptors, which explains its antiemetic properties. Olanzapine targets dopaminergic (D1, D2, D3, D4), serotonergic (5-HT2A, 5-HT2C, 5-HT3, 5-HT6), adrenergic (á1), histaminergic (H1), and muscarinic (m1, m2, m3, m4) receptors. Olanzapine has a benefit over combination CINV regimens in that it can target multiple key receptors with one medication. J Adv Pract Oncol. 2014 Jan-Feb; 5(1): 24–29.

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HER2-low Breast Cancer

Active 63-year-old, enjoys pickle ball, traveling, and spending time with her family

Diagnostic information: ER positive breast cancer (2007): ER+, PR+, HER2 2+, FISH nonamplified

*On **August 5, 2022**, the Food and Drug Administration approved **fam-trastuzumab deruxtecan-nxki (Enhertu)** for adult patients with unresectable or metastatic **HER2-low (IHC 1+ or IHC 2+/ISH-)** breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on **DESTINY-Breast04***

Diagnostics

6/2022: Reviewed initial pathology, patient with Her2 2+ disease indicating possible role for Enhertu.

Enhertu ordered as next line of therapy in light of HER2 2+ (low) and PFTs completed in 9/2022 in light of possible preparation given AE of possible associated ILD

5th line treatment

Enhertu approved, initiated on 11/16/22

Tolerating well overall, small right pleural effusion which was monitored

But course eventually complicated by nausea and erythroderma

Side effect management

Nausea managed by Palonsetron pre-medications with treatment.

Alternating of Zofran and Compazine OP with minimal control. Addition of Zyprexa with significant improvement.

Continue CT monitoring, clinical monitoring for AE and pulmonary decline

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Fam-trastuzumab deruxtecan

Premedication is recommended prior to infusion of fam-trastuzumab deruxtecan-nxki (ENHERTU)

Treatment option	Day 1	Days 2, 3, and 4
A (Preferred)[e]	Use the following: • Olanzapine[f] • NK1 RA • 5-HT3 RA[g,h] • Dexamethasone[i,j]	Use the following: • Olanzapine[f] on days 2-4 • Oral aprepitant on days 2-3 (if oral aprepitant is used on day 1) • Dexamethasone[i,j] on days 2-4
B	Use the following: • Olanzapine[f] • Palonosetron • Dexamethasone[i,j]	Use the following: • Olanzapine[f] on days 2-4
C	Use the following: • NK1 RA • 5-HT3 RA[g,h] • Dexamethasone[i,j]	Use the following: • Oral aprepitant on days 2-3 (if oral aprepitant is used on day 1) • Dexamethasone[i,j] on days 2-4

enhertu-therapy-management-guide.pdf (enhertuhcp.com)

Sacituzumab govitecan

Premedication recommended prior to each dose of TRODELVY for the following[1]:

To prevent chemotherapy-induced nausea and vomiting (CINV), premedicate with:

- Dexamethasone **AND**
- 5-HT3 receptor antagonist **OR** NK_1 receptor antagonist
- Other drugs as indicated

To prevent infusion reactions, premedicate with:

- Antipyretics
- H1 and H2 blockers
- Corticosteroids (for patients with a prior infusion reaction)

In patients with a prior excessive cholinergic reaction,* premedicate with:

- Atropine or other appropriate premedication

Medications and emergency equipment to treat infusion-related reactions including anaphylaxis should be available for immediate use.[1]

*Eg, abdominal cramping, diarrhea, salivation, etc.[1]

TRODELVY® (sacituzumab govitecan-hziy) | Resources for nurses (trodelvyhcp.com)

cornerstone specialty network™

Key Studies: Antibody Drug Conjugates

ADCs

DESTINY Studies: Fam-trastuzumab DXd

TROPICS Study: Sacituzumab govitecan

Patient Case Study

innovaTV 301 Study: Tisotumab vedotin

TROPION Study: Datopotamab DXd

Patient Case Study

cornerstone specialty network™

FDA APPROVALS

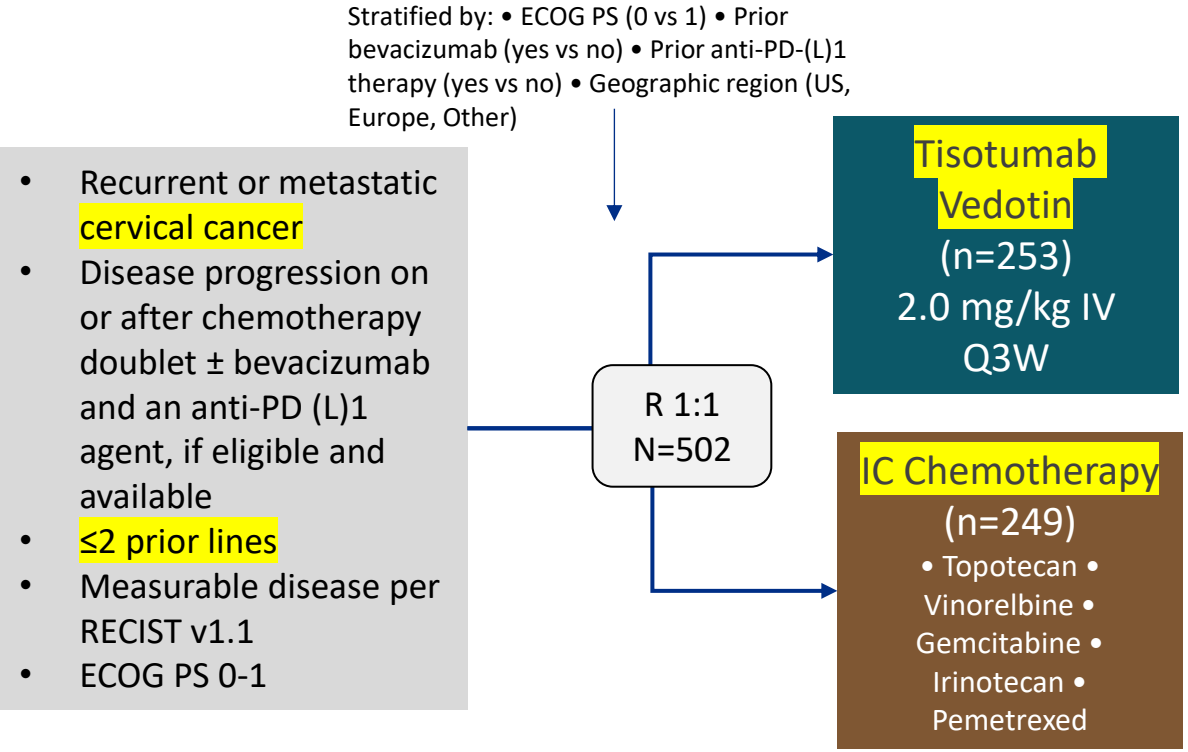
Tisotumab vedotin-tftv (TIVDAK)

- *On **April 29, 2024**, the FDA granted traditional approval to **tisotumab vedotin-tftv** (Tivdak, Seagen Inc. [now a part of Pfizer Inc.]) for recurrent or metastatic **cervical cancer** with disease progression on or after chemotherapy based on the innovaTV 301 trial.*
  - Tisotumab vedotin-tftv previously received accelerated approval for this indication on September 20, 2021.

KEY DATA

innovaTV 301

A Global, Randomized, Open-Label, Phase 3 Study of Tisotumab Vedotin vs Investigator's Choice of Chemotherapy in 2L or 3L Recurrent or Metastatic Cervical Cancer



Primary Endpoint • OS
Key Secondary Endpoints • PFSc • ORRc • Safety

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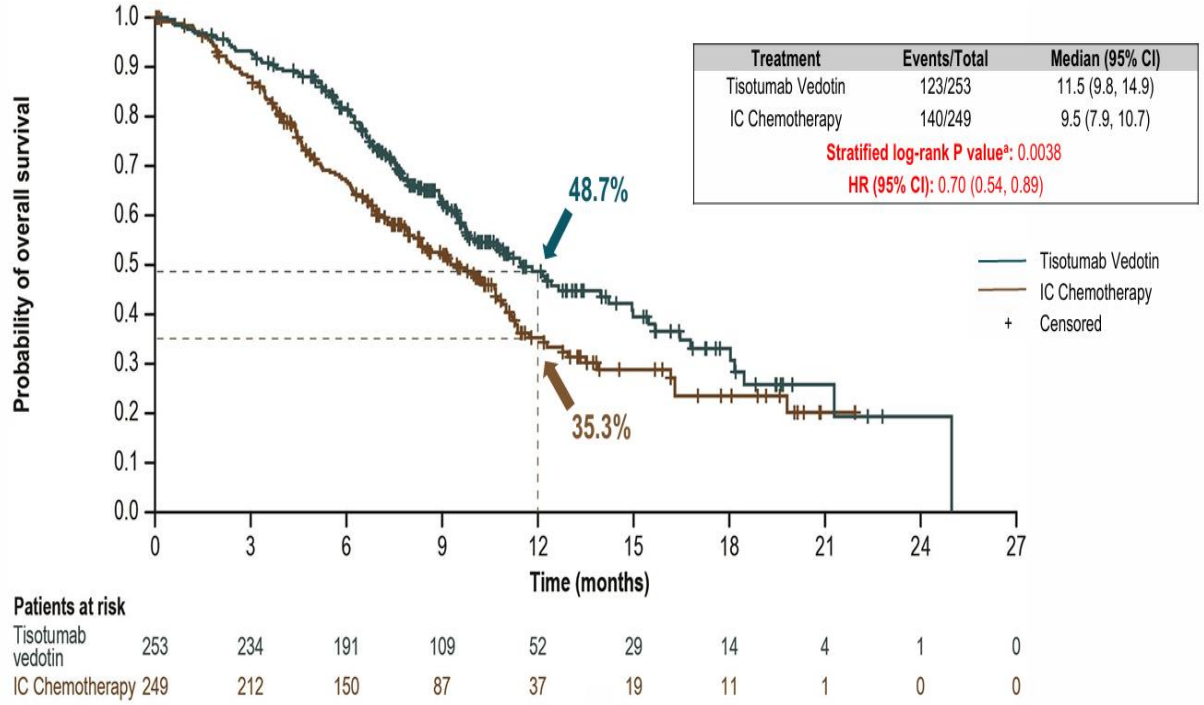
KEY DATA

innovaTV 301

Primary Endpoint: OS



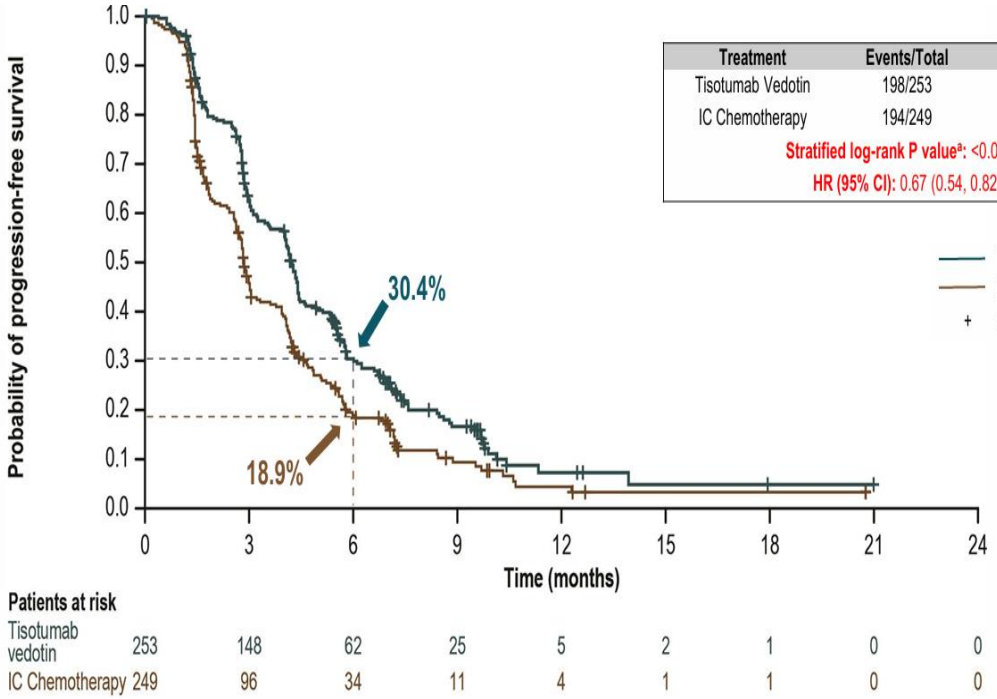
Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	123/253	11.5 (9.8, 14.9)
IC Chemotherapy	140/249	9.5 (7.9, 10.7)

Stratified log-rank P value[a]: 0.0038

HR (95% CI): 0.70 (0.54, 0.89)

[a]The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

Secondary Endpoint: PFS



Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	198/253	4.2 (4.0, 4.4)
IC Chemotherapy	194/249	2.9 (2.6, 3.1)

Stratified log-rank P value[a]: <0.0001

HR (95% CI): 0.67 (0.54, 0.82)

[a]The threshold for statistical significance is 0.0453 (2-sided), based on the actual number of PFS events at interim analysis.

In patients with recurrent cervical cancer, second- or third-line treatment with tisotumab vedotin resulted in greater efficacy than chemotherapy

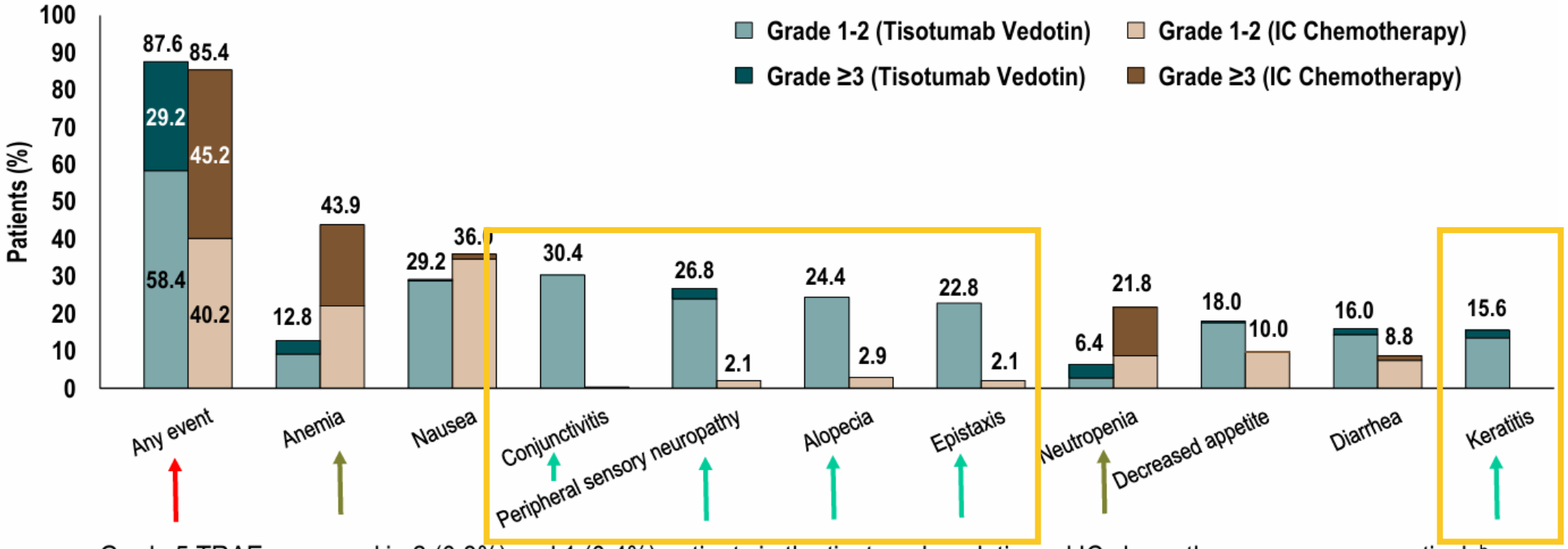
ESMO 2023 LBA9

KEY DATA

innovaTV 301: A Randomized, Open-Label, Phase 3 Trial

A Global, Randomized, Open-Label, Phase 3 Study of Tisotumab Vedotin vs Investigator's Choice of Chemotherapy in 2L or 3L Recurrent or Metastatic Cervical Cancer

Most Common Treatment-Related Adverse Events



- Grade 5 TRAEs occurred in 2 (0.8%) and 1 (0.4%) patients in the tisotumab vedotin and IC chemotherapy arms, respectively[b]
- Median relative dose intensity was 96.1% and 90.0% in the tisotumab vedotin and IC chemotherapy arms, respectively

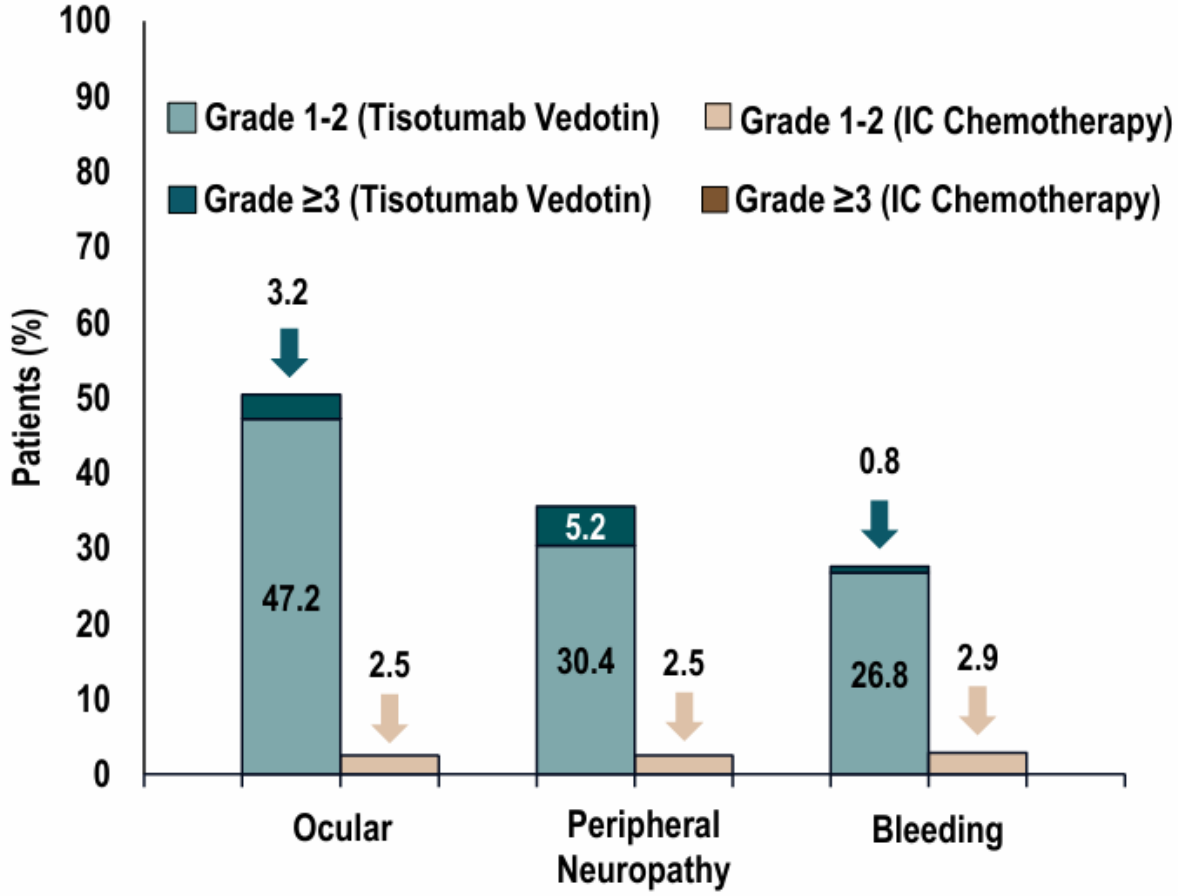
[a]TRAEs listed are those occurring in ≥15% of patients on either arm; [b]Grade 5 TRAEs included acute kidney injury (n=1) and Stevens-Johnson syndrome (n=1) in the tisotumab vedotin arm and pancytopenia (n=1) in the IC chemotherapy arm.

Tisotumab vedotin (Tivdak) can result in some unique adverse events but most are mild

KEY DATA

innovaTV 301: A Randomized, Open-Label, Phase 3 Trial

A Global, Randomized, Open-Label, Phase 3 Study of Tisotumab Vedotin vs Investigator's Choice of Chemotherapy in 2L or 3L Recurrent or Metastatic Cervical Cancer



AESI, adverse event of special interest
[a]Treatment-related AESIs

- There were no grade 4 or 5 AESIs
- Dose discontinuation due to ocular and peripheral neuropathy events occurred in 5.6% of patients for each

Three most common preferred terms for each AESI	
Ocular	Conjunctivitis (30.4%), keratitis (15.6%), dry eye (13.2%)
Peripheral neuropathy	Peripheral sensory neuropathy (26.8%), paresthesia (2.8%), muscular weakness (2.4%), peripheral sensorimotor neuropathy (2.4%)
Bleeding	Epistaxis (22.8%), hematuria (3.2%), vaginal hemorrhage (3.2%)

Ocular toxicities can be challenging; monitoring and management required

UNDER FDA REVIEW

Datopotamab deruxtecan

Datopotamab deruxtecan (Dato-DXd) Biologics License Application (BLA) has been accepted in the U.S. for:

- *the treatment of adult patients with **locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC)** who have received prior systemic therapy*
- *the treatment of adult patients with **unresectable or metastatic HR–positive, HER2-negative breast cancer** who have received prior systemic therapy for unresectable or metastatic disease*

Not yet approved

KEY DATA

TROPION-Breast01

Study Design: Randomized, phase 3, open-label, global study

Randomization stratified by:
- *Lines of chemotherapy in unresectable/metastatic setting (1 vs 2)*
- *Geographic location (US/Canada/Europe vs ROW)*
- *Previous CDK4/6 inhibitor (yes vs no)*

- HR-positive/HER2-negative BC (HER2-negative defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1-2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions[b]
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1-14 Q3W)
(n=367)

Endpoints:
- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

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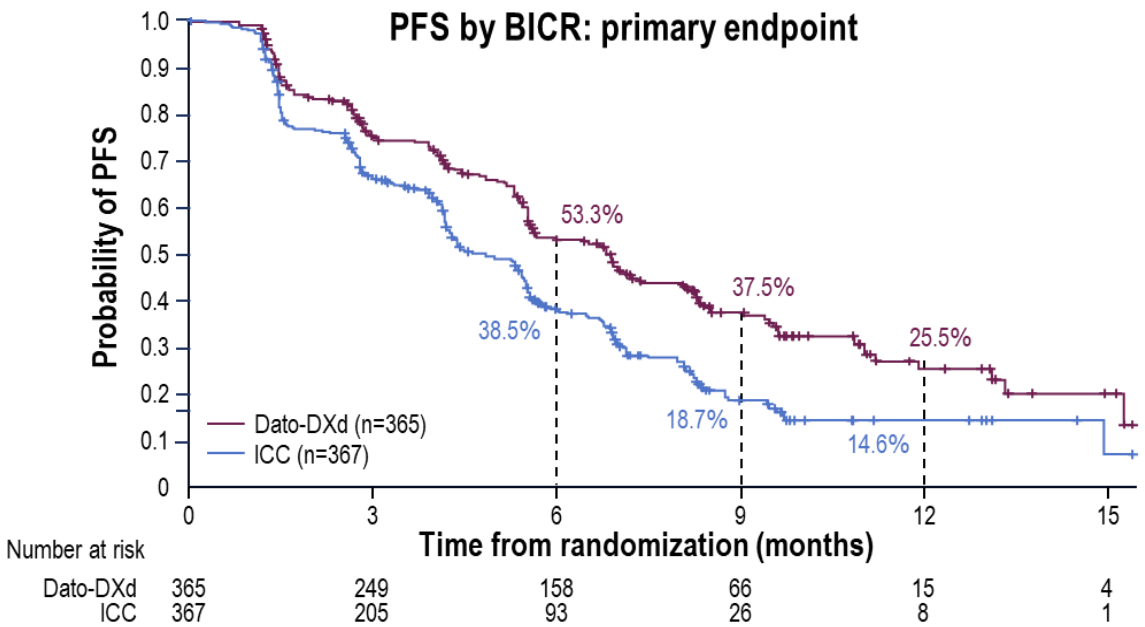
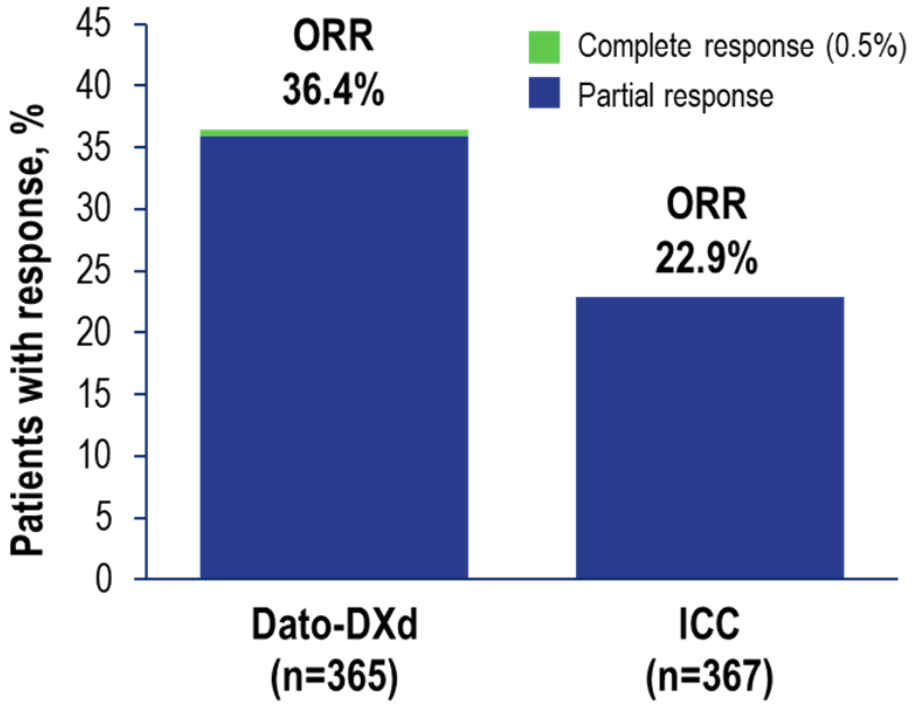
TROPION-Breast01

Efficacy





	Dato-DXd	ICC
Median PFS, months (95% CI)	**6.9** (5.7-7.4)	**4.9** (4.2-5.5)
Hazard ratio (95% CI)	**0.63 (0.52-0.76)**	
P value	<0.0001	

ICC = investigator choice of single agent chemo

Dato-DXd improved efficacy for patients with HR-positive/HER2-negative disease previously treated with 1-2 lines of chemotherapy compared to ICC

ESMO 2023. Abstr LBA11

KEY DATA

TROPION-Breast01

Overall Safety

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	**75 (21)**	**157 (45)**
Associated with dose reduction	**75 (21)**	**106 (30)**
Associated with dose interruption	**43 (12)**	**86 (25)**
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	**21 (6)**	**32 (9)**
Grade ≥3	**17 (5)**	**31 (8)**

Median treatment duration was 6.7 mo with Dato-DXd and 4.1 mo with ICC

Rate of grade ≥3 TRAEs in the Dato-DXd group was less than in the ICC group; Fewer TRAEs leading to dose reductions or dose interruptions with Dato-DXd compared with ICC

TRAEs Occurring in ≥15% of Patients

System Organ Class Preferred term, n (%	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatics system				
Anemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia[a]	39 (11)	4 (1)	149 (42)	108 (31)
Eye disorders				
Dry eye	**78 (22)**	2 (1)	27 (8)	0 (0)
Gastrointestinal				
Nausea	**184 (51)**	5 (1)	83 (24)	2 (1)
Stomatitis	**180 (50)**	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0 (0)	32 (9)	0 (0)
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0 (0)	72 (21)	0 (0)

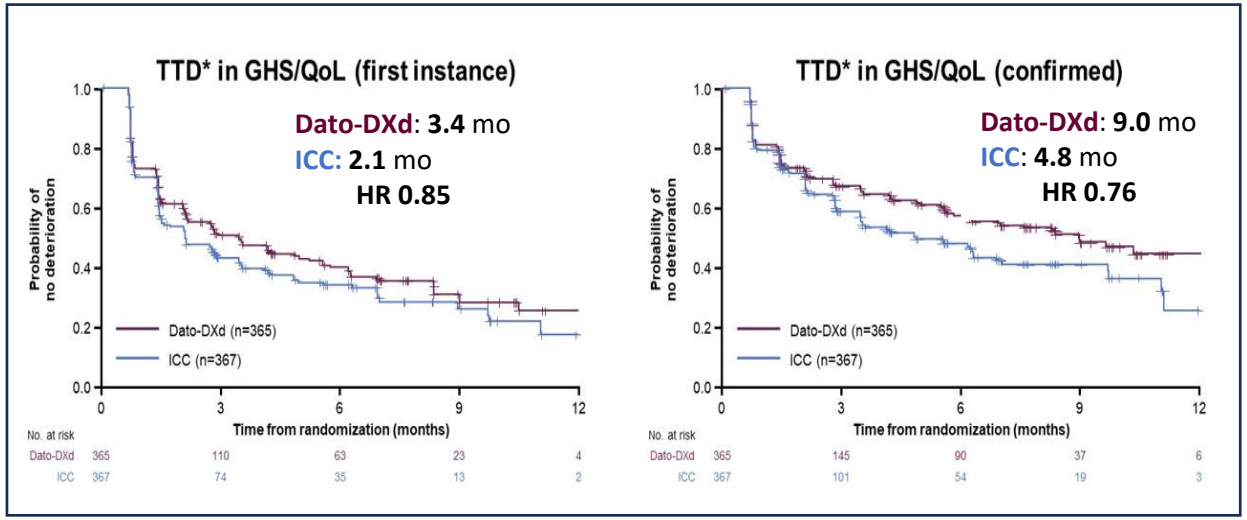
Eye disorders as well as gastrointestinal side effects with Dato-DXd noted; monitoring and management required

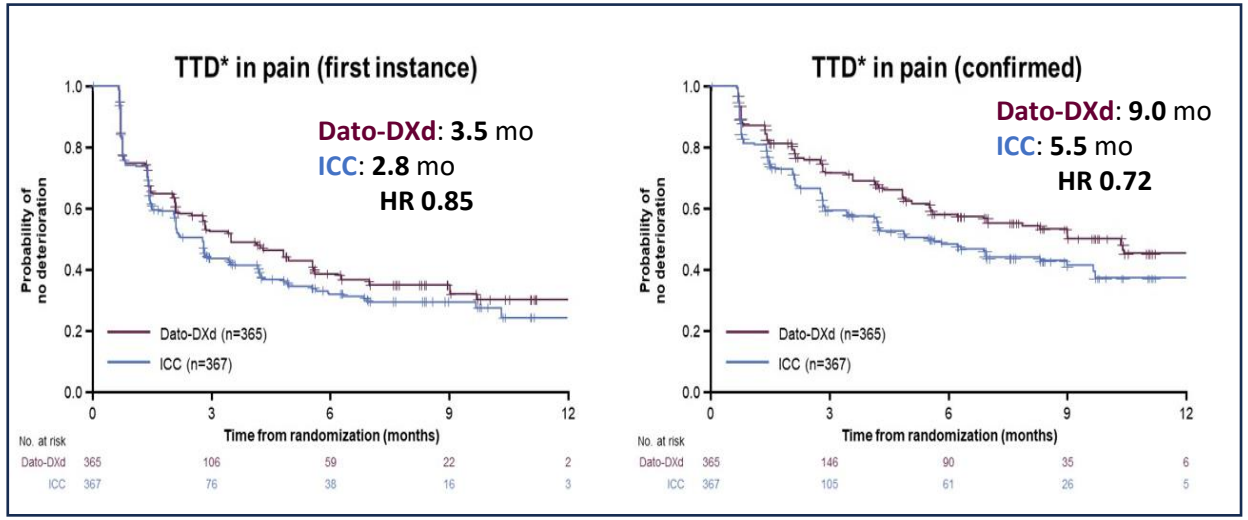
ESMO 2023. Abstr LBA11

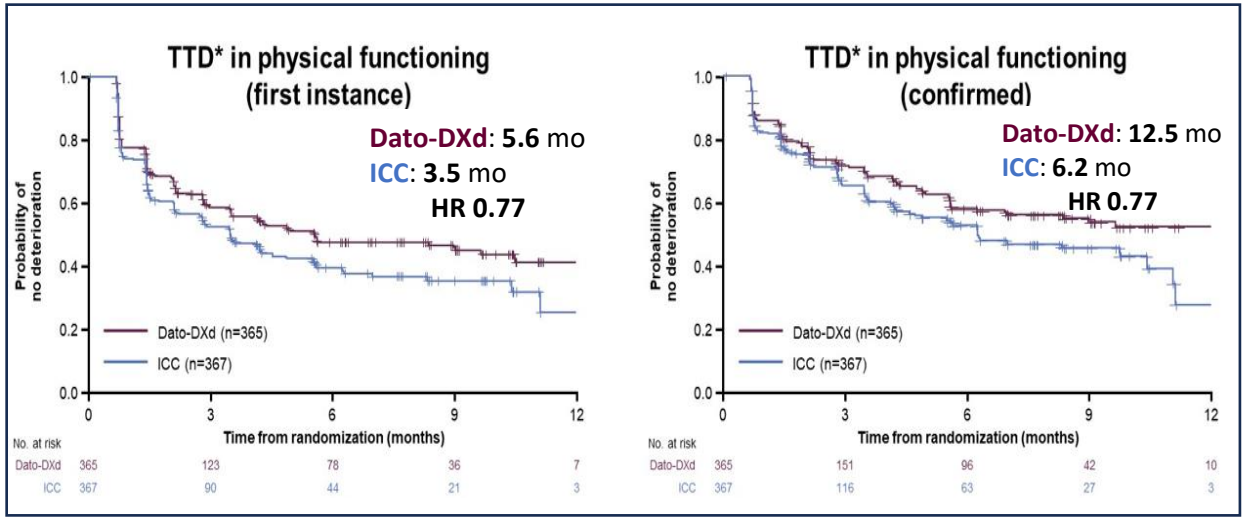
KEY DATA

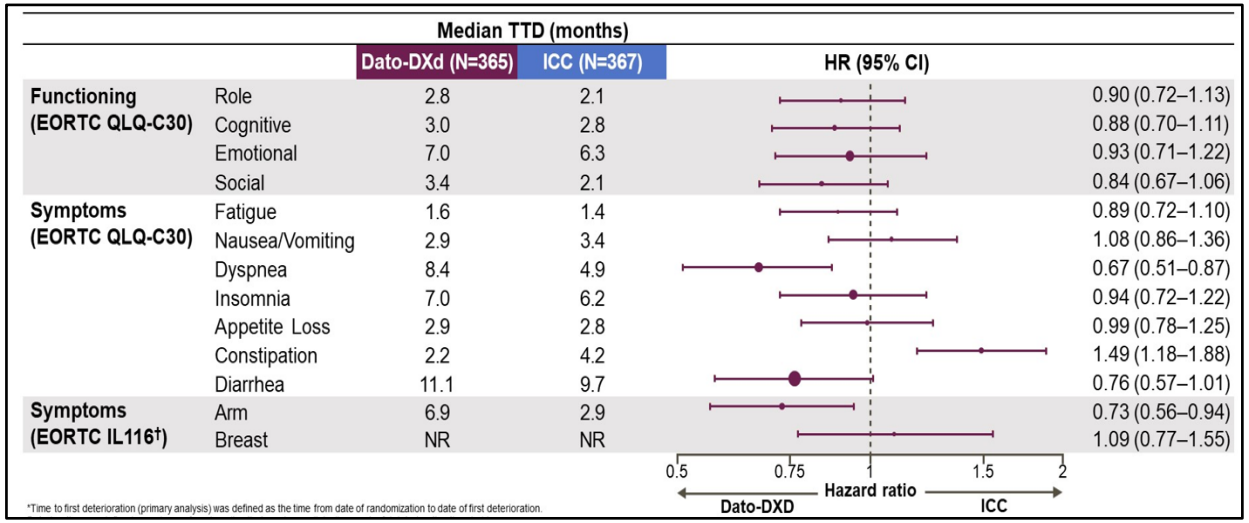
TROPION-Breast01: Dato-DXd vs chemotherapy in pts with HR+, HER2- mBC treated with 1-2 prior lines of chemotherapy

PRO data (median TTD for several parameters)









		Median TTD (months) Dato-DXd (N=365)	ICC (N=367)	HR (95% CI)
Functioning (EORTC QLQ-C30)	Role	2.8	2.1	0.90 (0.72–1.13)
	Cognitive	3.0	2.8	0.88 (0.70–1.11)
	Emotional	7.0	6.3	0.93 (0.71–1.22)
	Social	3.4	2.1	0.84 (0.67–1.06)
Symptoms (EORTC QLQ-C30)	Fatigue	1.6	1.4	0.89 (0.72–1.10)
	Nausea/Vomiting	2.9	3.4	1.08 (0.86–1.36)
	Dyspnea	8.4	4.9	0.67 (0.51–0.87)
	Insomnia	7.0	6.2	0.94 (0.72–1.22)
	Appetite Loss	2.9	2.8	0.99 (0.78–1.25)
	Constipation	2.2	4.2	1.49 (1.18–1.88)
	Diarrhea	11.1	9.7	0.76 (0.57–1.01)
Symptoms (EORTC IL116†)	Arm	6.9	2.9	0.73 (0.56–0.94)
	Breast	NR	NR	1.09 (0.77–1.55)

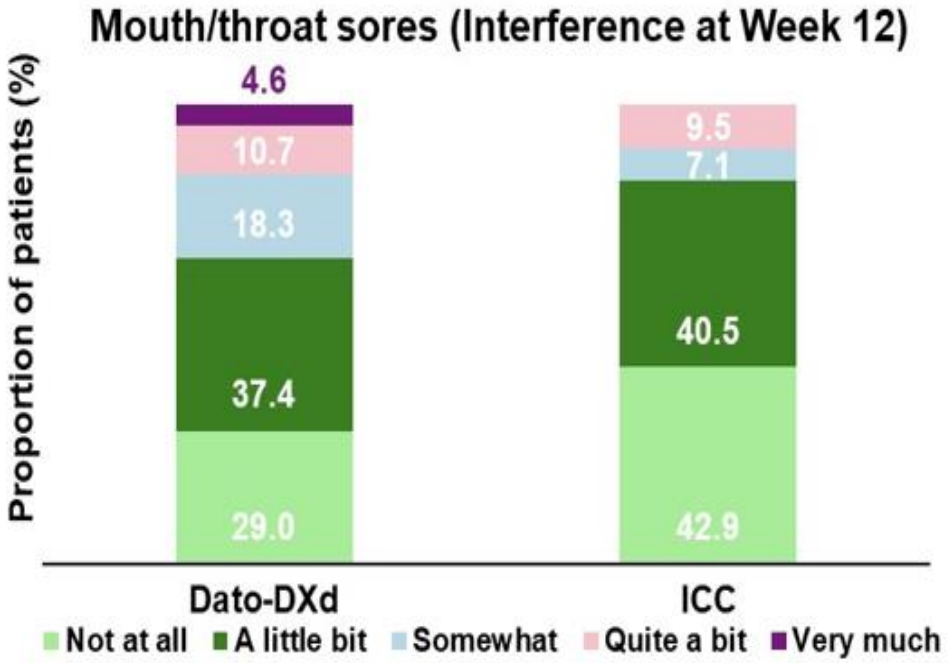
*Time to first deterioration (primary analysis) was defined as the time from date of randomization to date of first deterioration.

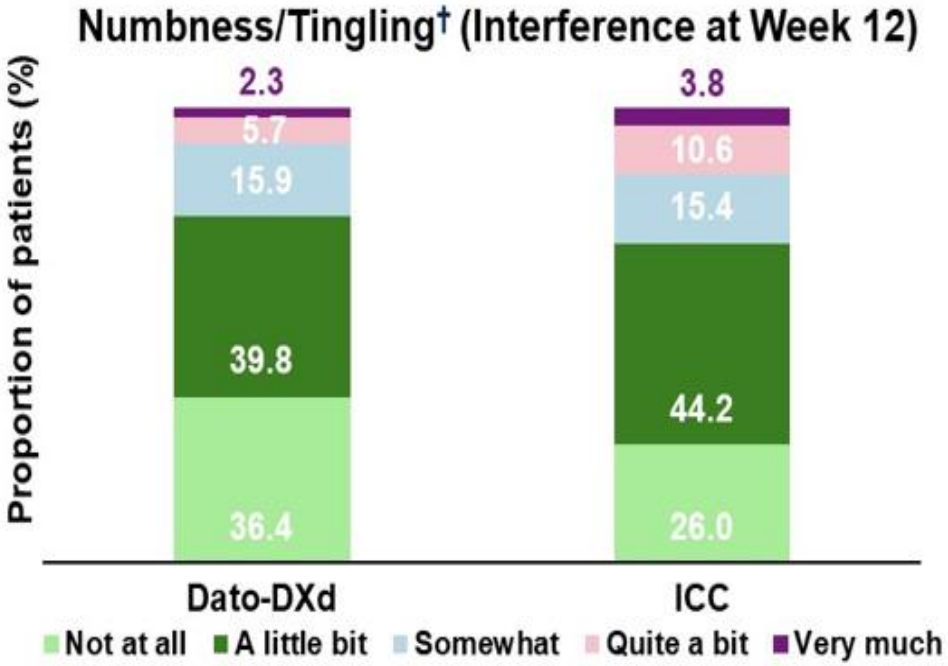
TTD = time to deterioration

KEY DATA

TROPION-Breast01

PRO details of 2 specific side effects: mouth sores and numbness/tingling





PRO data further support Dato-DXd as a potential treatment option for patients with HR+, HER2- mBC; after chemo

ASCO 2024. Abstr. 1025

Patient Case Study

Erica Deenihan

Cervical Cancer

Active 50-year-old, working mother of 2 teenage kids

Diagnostic information: Initially likely stage IIIC disease with LN involvement on PET and MRI (2020)

1st line treatment

Definitive treatment with chemo/RT: Initiated weekly Cisplatin 40mg/m2 with concurrent RT

Incidental CT showed growth in multiple LN : surprising rapid growth in 2 weeks

2nd line treatment

Cisplatin/paclitaxel with MVASI (bevacizumab)

Inguinal biopsy negative.

Mesenteric biopsy consistent with mets

Response in lymphadenopathy after 3 cycles

3rd line treatment

Internal radiation set for 3/5/2021 insertion then treatment 3/12 and 3/19

s/p: chemo break, back on carbo/taxol/avastin 4/2021.

Stable disease on imaging 6/2021

Progression in 8/2021

4th line treatment

8/2021, started Keytruda

PD-L1: 2%

1/2022 Progressing omental and mesenteric LN

What next?

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma		
Chemoradiation[b]	Recurrent or Metastatic Disease	
	First-line Therapy[b,f]	Second-line or Subsequent Therapy[j]
Preferred Regimens • Cisplatin[c,d,1] • Carboplatin if patient is cisplatin intolerant[c,d] **Other Recommended Regimens[e] (if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[2] • Gemcitabine[3] • Paclitaxel[4,5]	**Preferred Regimens** • PD-L1–positive tumors ▸ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)[d,g,h,i,6] ▸ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)[d,g,h,i,6] • Cisplatin/paclitaxel/bevacizumab[d,g,7] (category 1) • Carboplatin/paclitaxel/bevacizumab[d,g] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[8,9] • Carboplatin/paclitaxel[10,11] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,g,7,12] (category 1) • Topotecan/paclitaxel[12] • Cisplatin/topotecan[12] • Cisplatin[9] • Carboplatin[13,14]	**Preferred Regimens** • Pembrolizumab for TMB-H tumors[h,k] or PD-L1–positive[i] or MSI-H/dMMR tumors[h,15] • Tisotumab vedotin-tftv[16] • Cemiplimab[h,17] **Other Recommended Regimens** • Bevacizumab[g] • Paclitaxel[14,18] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[h,i,19] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[20] • RET gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

NCCN Guidelines preferred recommendations for second-line or subsequent therapy

All recommendations are category 2A unless otherwise indicated

Note: Cemiplimab is not yet FDA approved for cervical cancer

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TIVDAK® (tisotumab vedotin-tftv)

Patient discussion on adverse events associated with treatment:

- hemoglobin decreased
- fatigue
- lymphocytes decreased
- nausea
- peripheral neuropathy
- alopecia
- epistaxis
- conjunctival adverse reactions
- hemorrhage
- leukocytes decreased
- creatinine increased
- dry eye
- prothrombin international normalized ratio increased
- activated partial thromboplastin time prolonged
- diarrhea
- rash

Product labeling includes a boxed warning for ocular toxicity.

WARNING: OCULAR TOXICITY

See full prescribing information for complete boxed warning.

- **TIVDAK can cause severe ocular toxicities resulting in changes in vision, including severe vision loss and corneal ulceration. (5.1)**
- **Conduct an ophthalmic exam, including an assessment of ocular symptoms, visual acuity, and slit lamp exam of the anterior segment of the eye prior to initiation of TIVDAK, prior to every cycle for the first nine cycles, and as clinically indicated. (2.2, 5.1)**
- **Adhere to the required premedication and eye care before, during, and after infusion. (2.2)**
- **Withhold TIVDAK until improvement and resume, reduce the dose, or permanently discontinue, based on severity. (2.3, 5.1)**

- Establish optometrist/optho for supportive management while on tx
- Educate/initiate appropriate eye care

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Cervical Cancer

Active 50-year-old, working, mother of 2 kids

Diagnostic information: Initially likely stage IIIC disease with LN involvement on PET and MRI (2020)

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Progression in 8/2021

4th line treatment

8/2021, started Keytruda

PD-L1: 2%

1/2022 Progressing omental and mesenteric LN

5th line treatment

Started Tivdak

Ophthalmic exam with each dose, brimonidine, dex and hydrating drops and ice pack reviewed

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TIVDAK® (tisotumab vedotin-tftv)

Monitor for new or worsening ocular signs and symptom, including but not limited to:

- Dry eyes
- Eye redness
- Eye irritation
- Light sensitivity
- Blurred vision
- Vision loss or impairment

TivdakHCP_Eye_Care_Provider_Guide.pdf

1

Before infusion:

- Referral to optometrist or ophthalmologist prior to initiation of TIVDAK and prior to every cycle for the first 9 cycles, and as clinically indicated and prescribe eye drops [Corticosteroid eye drops, Vasoconstrictor eye drops, Lubricating eye drops (over the counter)]

2

Prior to infusion:

- **The care team should instruct the patient to apply corticosteroid drops (1 drop per eye, or as prescribed)**
- **The care team should instruct the patient to apply vasoconstrictor drops immediately prior to the infusion (3 drops per eye, or as prescribed)**
- **After administration of eye drops, the care team may assist the patient in placing cold packs over the eye area ~10 minutes prior to the infusion, during the infusion, and for 20 minutes after, keeping the eye area cool for a total of 60 minutes**

3

After infusion:

- Patient will continue applying corticosteroid drops (1 drop per eye) two more times throughout the infusion day, or as prescribed
- Days 2-3: Patient will apply corticosteroid drops (1 drop per eye) three times per day, or as prescribed

4

Throughout treatment:

- **The care team should proactively monitor for new or worsening ocular adverse reactions throughout treatment with Tivdak, and encourage patient to check their eyes daily and report any symptoms**
- Patient should apply lubricating drops as needed for the duration of therapy and for 30 days after the last dose of Tivdak
- Patient should avoid contact lenses and eye irritants throughout treatment with Tivdak unless directed otherwise

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The Eye Drop Schedule

tivdak
tisotumab vedotin-tftv
for injection 40 mg

Tivdak Required Eye Care[1,2]

DURING AND AFTER INFUSION

Day 1: Infusion Day (once every 3 weeks)

Pre-Infusion (~10 min prior)	**Corticosteroid Eye Drops** 1 drop per eye or as prescribed	**Vasoconstrictor Eye Drops** 3 drops per eye immediately prior to infusion or as prescribed	**Cold Packs** Rotate as needed to keep eye area cool for 60 minutes total
During Infusion (~30 min)	**Infusion** 2.0-mg/kg intravenous infusion	**Cold Packs** Rotate as needed to keep eye area cool for 60 minutes total	
After Infusion (~20 min)	**Cold Packs** Rotate as needed to keep eye area cool for 60 minutes total		
Remainder of Day	**Corticosteroid Eye Drops** 1 drop per eye 2x throughout the remainder of the day or as prescribed **(Instruct patients to self-administer)**		

tivdak
tisotumab vedotin-tftv
for injection 40 mg

Tivdak® Required Eye Care[1,2]

DURING AND AFTER INFUSION (CONTINUED)

Post Infusion Day (patient-driven tasks)	DAY 2	DAY 3	ONGOING
Corticosteroid Drops 1 drop per eye, 3x per day for Days 2-3 (72 hours) after infusion or as prescribed	S	S	
Lubricating Drops Instruct patients to administer for the duration of therapy and for 30 days after the last dose of Tivdak	L	L	L
Eye Self-Check Encourage patients to monitor their eyes daily and call their eye care provider and/or your office in the event of new or worsening ocular signs and symptoms			
Avoid Contact Lenses Advise patients to avoid wearing contact lenses throughout treatment unless directed to do so by an eye care provider			

1. Apply cold packs fully over the eye and nose area following administration of the vasoconstrictor drops and to leave on during infusion, changing as needed to ensure maximum coldness
2. Ensure proper optho follow ups after each administration
3. Eye Care checklist in support kit

TivdakHCP_Dosing_Administration_and_Eye_Care_Guide.pdf

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Nurse Symposium

Antibody Drug Conjugates

Bispecific Antibodies

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ADCs versus Bispecific antibodies

Antibody-drug conjugates (ADCs) and bispecific antibodies (BsAbs) are both targeted cancer therapies, but they operate through different mechanisms

- ADCs consist of an antibody linked to a cytotoxic drug, which is delivered directly to cancer cells
- ADCs deliver toxic payloads directly to cancer cells

- Bispecific antibodies simultaneously bind to two different antigens, triggering immune responses against cancer cells
- Bispecific antibodies engage the immune system to target and kill tumor cells

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Bispecific Antibodies

In Community Oncology, what are the top challenges?

1. ***Complexity and novelty***
2. ***Limited clinical experience***
3. *Treatment-related toxicities*
4. *Transition from in-patient to out-patient setting*

What are ways to best integrate bispecifics into community practice?

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Bispecific (BsAbs) Antibodies and CAR T-Cell Therapy

Efficacy and safety

- **CAR T**: long-term survival data and duration of therapy
- **Bispecifics**: lower toxicity

Accessibility

- **CAR T**: administered at a specialized center
- **Bispecifics**: off the shelf availability and easier access

Cost

- **CAR T**: higher upfront cost
- **Bispecifics**: overall, comparable in cost

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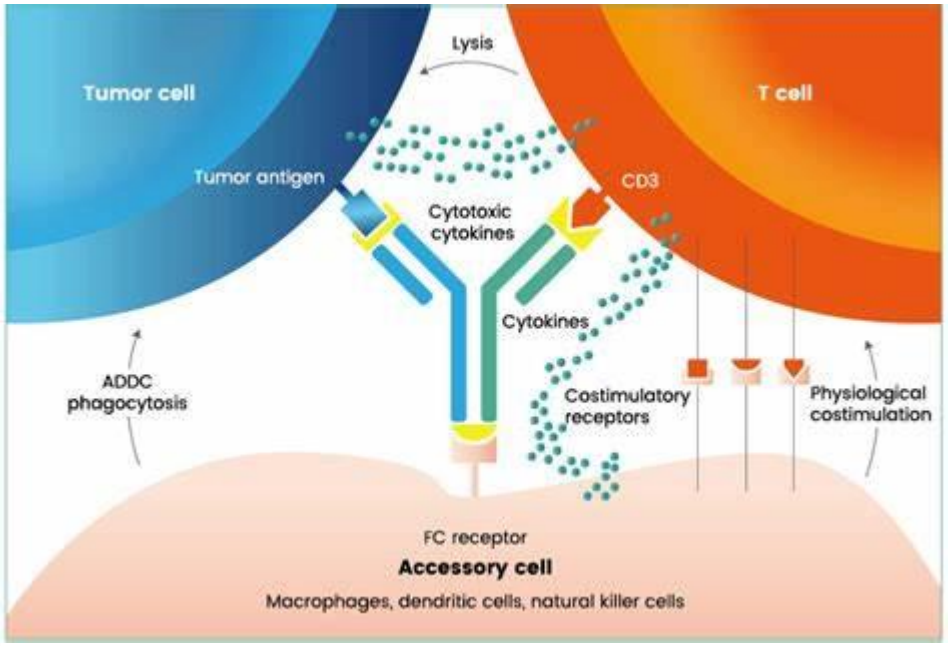
The Specifics of Bispecific Antibodies (BsABs)

Bispecific antibodies (BsAbs) have two distinct binding domains that can bind to two antigens or two epitopes (an antigen part) present on cancer cells and T cells simultaneously

Antibody-dependent cellular cytotoxicity (ADCC) is central to the immune response to cancer cells. In this process, antibodies bound to antigens on the surface of cancerous cells recruit and activate effector immune cells, such as natural killer cells, for tumor recognition and elimination

Bispecific antibodies recruit T cells by binding CD3 to cancer cells, leading to the secretion of cytokines, granzyme, perforin and ultimately leading to the killing of cancer cells



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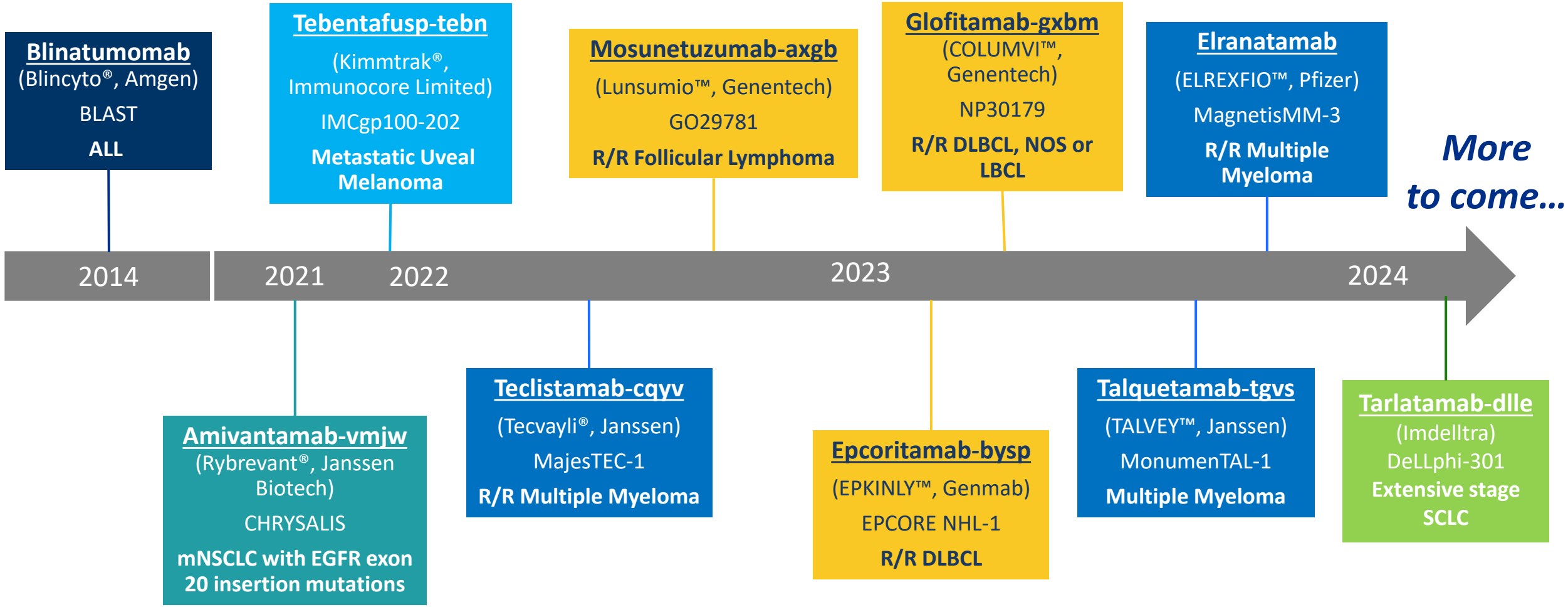
Bispecifics: Developmental Timeline in Oncology



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Bispecifics: Box Warnings* and Warnings and Precautions

BLINCYTO
- Cytokine Release Syndrome (CRS)*
- Neurological toxicities
- Infections
- Effects on Ability to Drive and Use Machines
- Pancreatitis

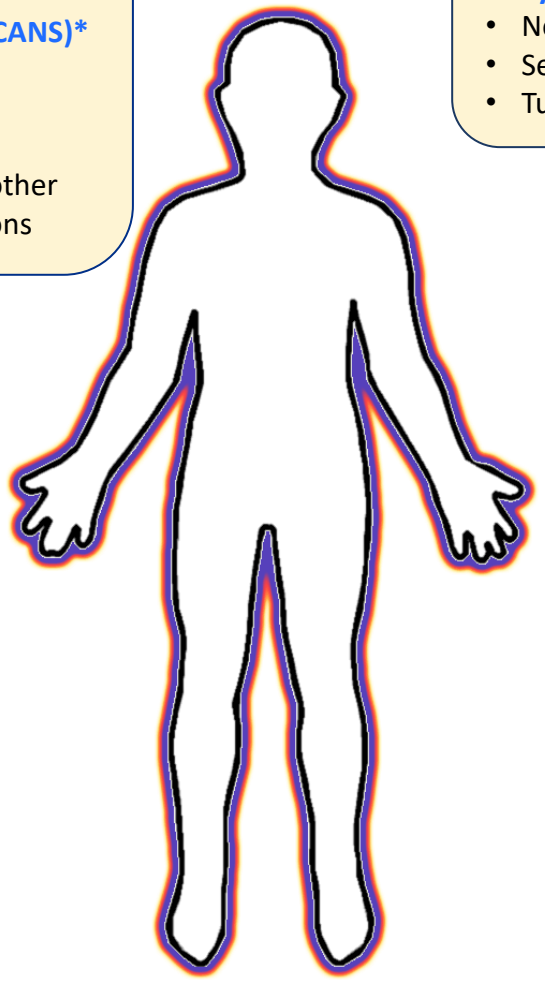
TECVAYLI
- Cytokine release syndrome (CRS)*
- Neurologic toxicity (ICANS)*
- Hepatotoxicity
- Infections
- Neutropenia
- Hypersensitivity and other administration reactions

COLUMVI
- Cytokine Release Syndrome (CRS)*
- Neurologic Toxicity
- Serious Infections
- Tumor Flare

IMDELLTRA
- Cytokine release syndrome (CRS)*
- Neurologic toxicity (ICANS)*
- Cytopenias
- Infections
- Hepatotoxicity
- Hypersensitivity

KIMMTRAK
- Cytokine Release Syndrome (CRS)*
- Skin reactions
- Elevated liver enzymes

LUNSUMIO
Cytokine release syndrome (CRS)*
- Neurologic Toxicity
- Infections
- Cytopenias
- Tumor Flare



TALVEY
- Cytokine release syndrome (CRS)*
- Neurologic toxicity (ICANS)*
- Oral Toxicity and Weight Loss
- Infections
- Cytopenias
- Skin Toxicity
- Hepatotoxicity

ELREXFIO
- Cytokine release syndrome (CRS))*
- Neurologic toxicity (ICANS)*
- Infections
- Neutropenia
- Hepatotoxicity

RYBREVANT
- Infusion-Related Reactions (IRR)
- Interstitial Lung Disease (ILD)/Pneumonitis
- Dermatologic Adverse Reactions
- Ocular Toxicity

EPKINLY
- Cytokine release syndrome (CRS)*
- Neurologic toxicity (ICANS)*
- Infections
- Cytopenias

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Note: Embryo-fetal toxicity in all warnings and precautions

Bispecific Antibodies

In Community Oncology, what are the top challenges?

1. *Complexity and novelty*
2. *Limited clinical experience*
3. ***Treatment-related toxicities***
4. *Transition from in-patient to out-patient setting*

What are ways to best integrate bispecifics into community practice?

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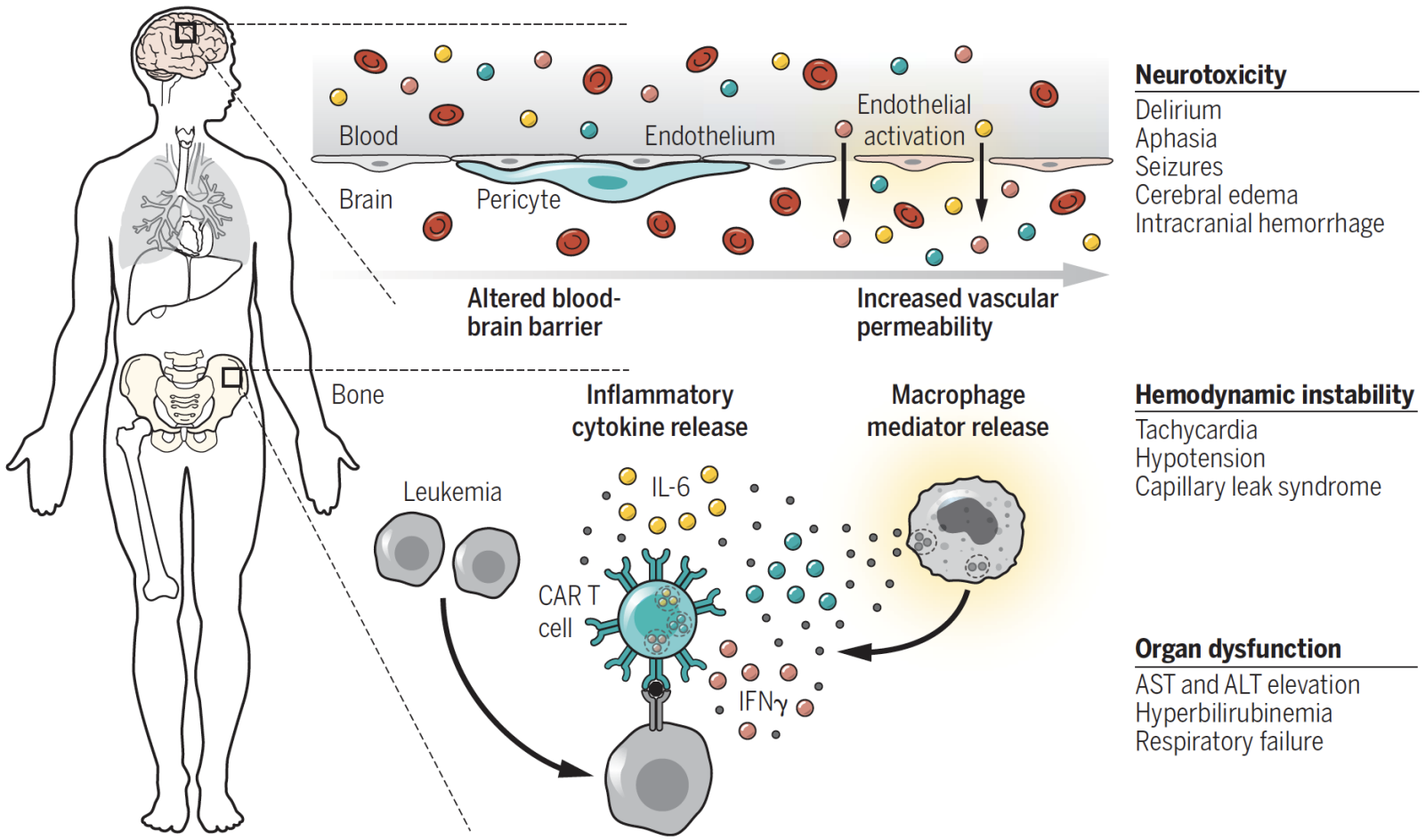
Treatment associated cytokine release syndrome (CRS) and neurotoxicity (ICANS*)



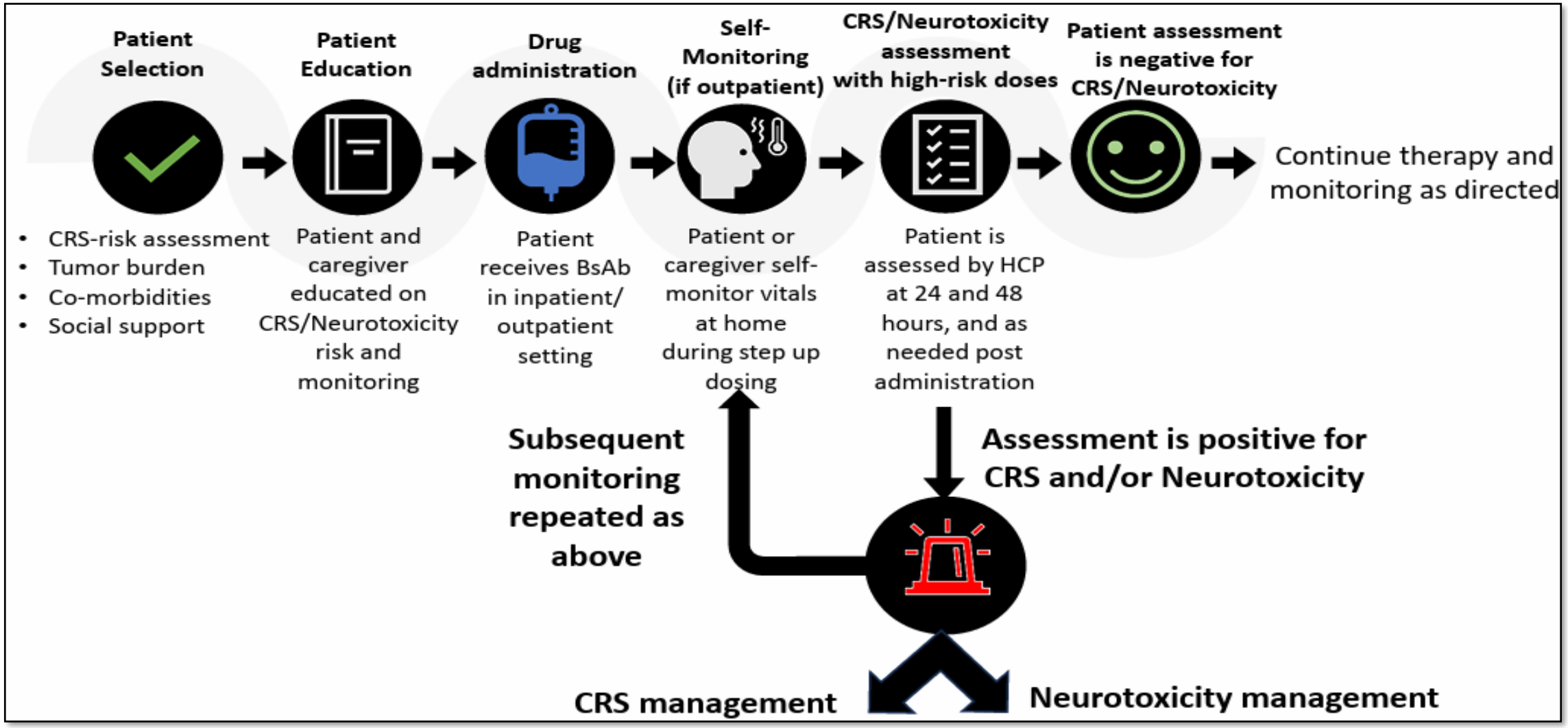
June et al., Science. 2018 Mar 23;359(6382):1361-1365.

BsAbs have a relatively short half-life (compared to CAR T-cell therapy) and need to be administered repeatedly

Side effects tend to resolve quickly with BsAbs, which is beneficial in managing the overall treatment process. This rapid resolution of side effects is likely due to the short half-life of BsAbs, allowing for quick clearance from the body

*ICANS: immune effector cell-associated neurotoxicity syndrome

Bispecific Antibody (BsAb) Management



Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy
Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
			With	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or	
Hypoxia	None	Requiring low-flow nasal cannulaz or blow-by	Requiring high-flow nasal can nulaz, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Premedication reduces CRS rates

Steroids

Tocilizumab

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

D.W.Lee et al./BiolBloodMarrowTransplant 25 (2019): 625-638

Incidence of CRS with teclistamab in MajesTEC-1 over time by grade

EXAMPLE:

Overall incidence of CRS with teclistamab in MajesTEC-1 for R/R Multiple Myeloma

- CRS occurred in 72.1% of patients (N=119/165) with the majority being:
  - **Grade 1 (50.3%)**
  - Grade 2 (21.2%)
- Most CRS occurred after:
  - Step-up dose 1 – 43.6%
  - Step-up dose 2 – 35.2%
  - Cycle 1 Day 1 - 24.2%
  - Cycle 1 Day 8 – 4.8%
  - Cycle 1 Day 15 – 2.4%
  - Cycle 2+ - 3.6%
- Only 1 percent of patients experienced CRS in subsequent cycles

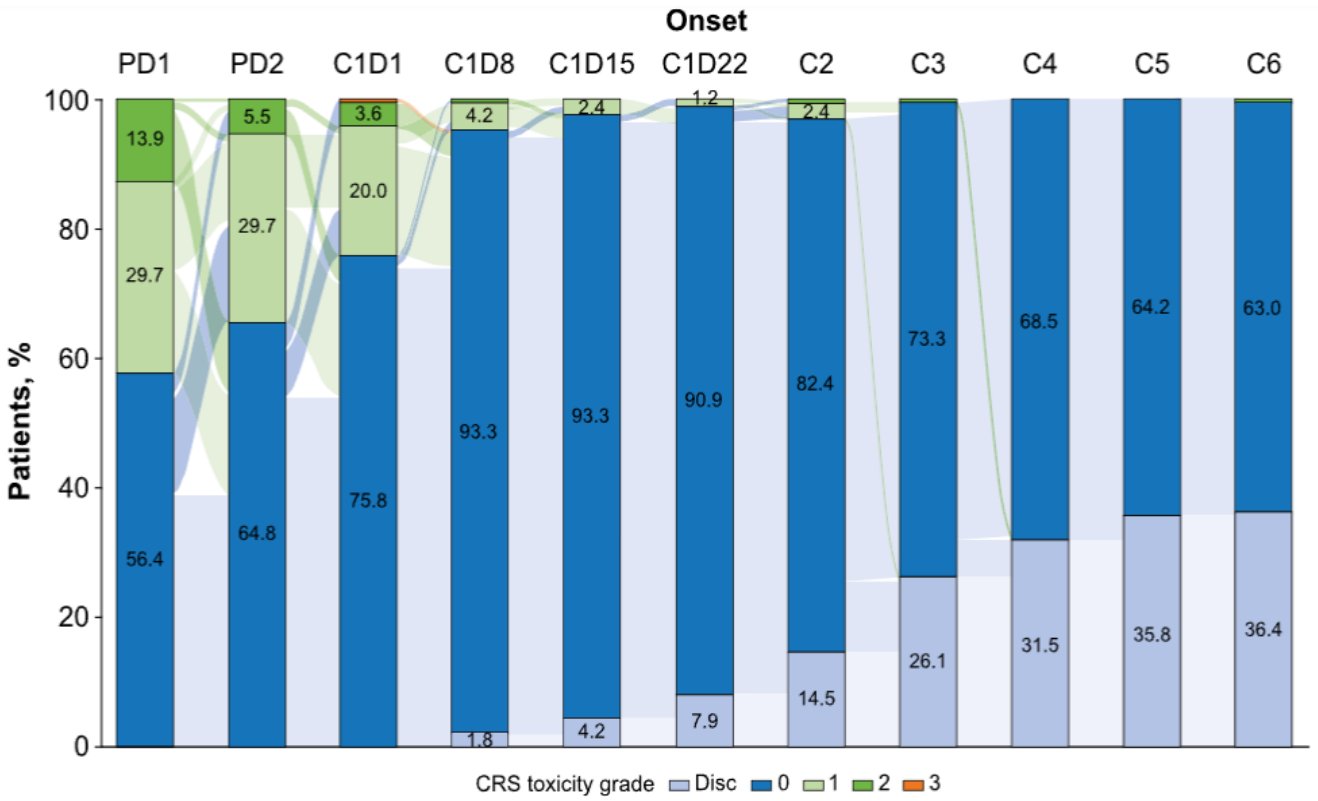


FIGURE 1 Incidence of CRS with teclistamab in MajesTEC-1 over time by grade. CRS was graded according to American Society for Transplantation and Cellular Therapy criteria.[6] If a patient had more than one event at a time point, the maximum grade is used. Repeat step-up before C1 is not displayed. One patient had a grade 1 CRS event after a repeat step-up dose before C1. No patients discontinued the study due to a CRS event. C indicates cycle; CRS, cytokine release syndrome; D, day; Disc, discontinued; PD, priming (step-up) dose.

Cancer. 2023;129:2035–2046.

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Key points for CRS

***Definition**: CRS is an acute systemic inflammatory syndrome characterized by fever and organ dysfunction*

***Symptoms:** fever (required) with possible hypoxia, hypotension, tachypnea, nausea, headache, fatigue, myalgias, or malaise*

- *Educate staff and develop toxicity management protocols*
- *In-person evaluation*
- *Consider daily dexamethasone for Grade 1; Ensure tocilizumab is available*
- *Early tocilizumab after trial of dexamethasone should be considered for patients with multiple medical risk factors (e.g., comorbidities)*
- *Grade 2 and beyond: inpatient management recommended*
- *Ensure emergency department staff and hospitalists are aware that an on-call physician is available to help manage any patient who may present with CRS*

Educate patients and their caregivers about signs and symptoms of CRS

*The **NCCN Guidelines** for the Management of Immunotherapy-Related Toxicities includes a section on **CRS** for patients treated with **CAR T-cell therapy** but **does not** include a section on CRS for patients treated with bispecific antibodies*

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Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

ASTCT ICANS Consensus Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or gen eralized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerbrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event

Steroids

Tocilizumab / Anakinra

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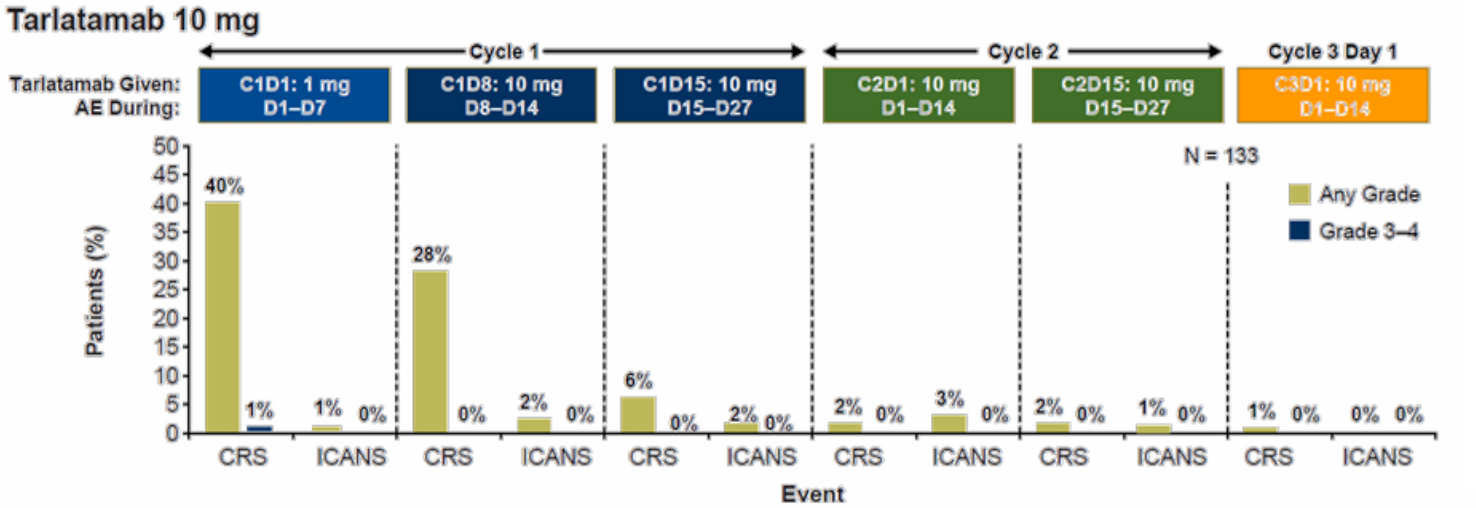
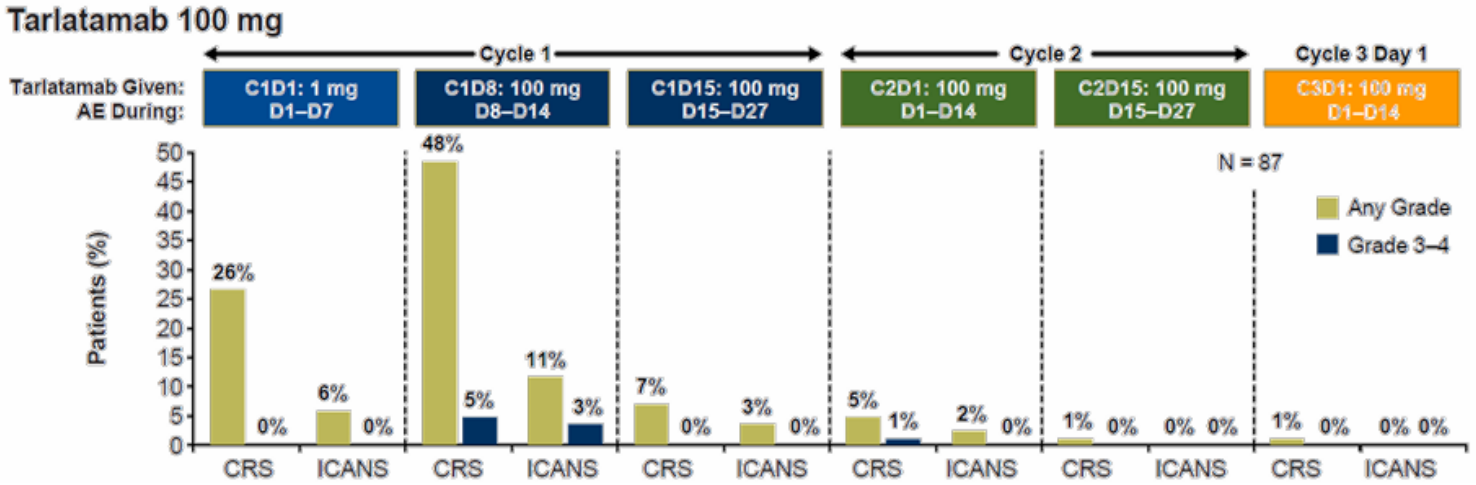
Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy
Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

Incidence of CRS and ICANS with tarlatamab over time by grade: DeLLphi-301





- CRS was largely confined to the first or second dose (C1D1 or C1D8), primarily grade 1–2
- ICANS* occurred infrequently overall and was predominantly observed with tarlatamab 100 mg

CRS interventions:

Patients receiving tarlatamab, n (%)	10 mg (n = 133)	100 mg (n = 87)
Tocilizumab	7 (5)	9 (10)
Supplemental oxygen	11 (8)	8 (9)
Vasopressor support	1 (1)	1 (1)

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ESMO 2023 LBA92

Ahn MJ, et al. N Engl J Med. 2023;389:2063-2075.

Key points for ICANS

*The **NCCN Guidelines** for the Management of Immunotherapy-Related Toxicities includes a section on **neurotoxicity** for patients treated with **CAR T-cell therapy** but **does not** include a section on neurotoxicity for patients treated with bispecific antibodies*

***Definition:** neurological AEs after BsAb therapy most frequently consist of headache and dizziness; occasionally, ICANS-like symptoms occur; these may or may not accompany CRS*

***Symptoms:** delirium, dysgraphia, tremor, lethargy, difficulty concentrating, agitation, confusion, expressive aphasia, apraxia, depressed level of consciousness, encephalopathy, and seizures*

- *Early intervention is critical to be able to give the next dose*
- *Perform ICE score on all patients with neurologic symptoms: assess for alternate cause of symptoms; consider performing CT head, EEG, MRI, or LP, as appropriate*
- *Avoid concurrent medications that might cause cognitive changes*
- *Assess for concurrent symptoms of CRS (fever, hypoxia, and hypotension); treatment of CRS can occur concurrently if appropriate*
- *Grade 1: ICE 7-9 - consider observation or close monitoring in outpatient setting. Can consider dexamethasone; increase the dose (dexamethasone, anakinra) if not responding*
- *Grade 2 and beyond: inpatient management recommended*

Educate patients and their caregivers about signs and symptoms of ICANS

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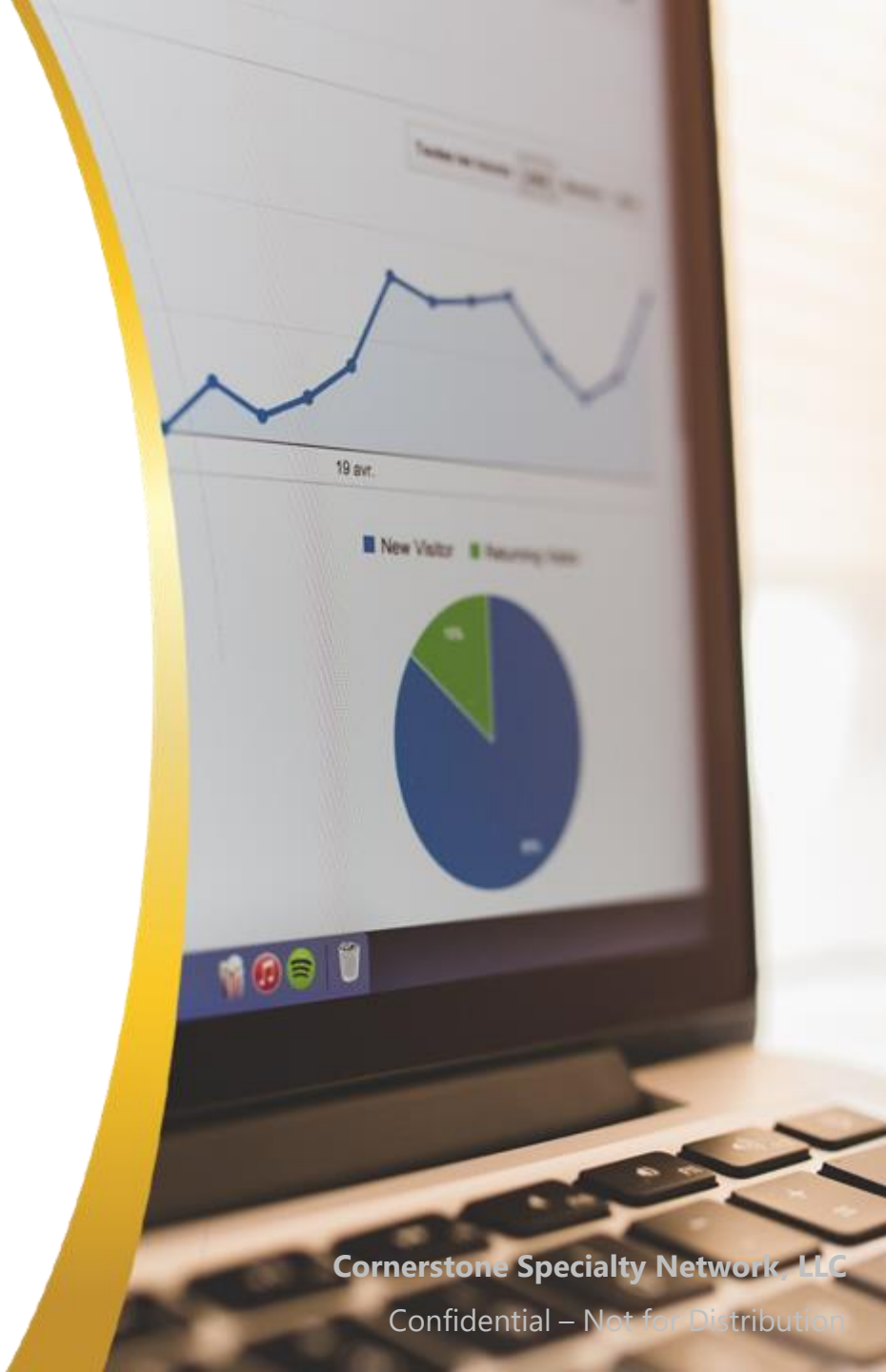
Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy Blood. 2024 Jan 22:blood.2023022432. doi: 10.1182/blood.2023022432. Online ahead of print.

Polling Question 5

What resources are you currently using for bispecific patient education?

- Pharma-provided: website/printables/handouts
- NCCN Guidelines for patients
- Oncology nursing websites
- Other



Bispecific Antibodies

In Community Oncology, what are the top challenges?

1. *Complexity and novelty*
2. *Limited clinical experience*
3. *Treatment-related toxicities*
4. ***Transition from in-patient to out-patient setting***

What are ways to best integrate bispecifics into community practice?

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Transition from in-patient to out-patient setting

Importance of timely consultation and communication around patient urgency when transferring between community and hospital setting

Establish strong relationships between HCPs working at academic and community cancer programs

- Build on existing referral pathways
- Ensure staff are familiar with referral process

Utilize online resources to help prepare/educate patients

- Provide patient information sheet

Use telehealth to provide follow-up care and monitor for symptoms

Use knowledgeable navigators (provide training) to coordinate logistics between community and academic medical centers

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Checklist Prior to Starting Bispecifics

Patient Education & Caregiver: a must!

Wellness Tools: Basic Thermometer, BP instrument and Pulse Oximeter

Clear guidance: a flowchart with vitals log

Prescription: Dexamethasone (and acetaminophen and diphenhydramine)

Prophylaxis: Bactrim and Acyclovir

Assess comorbidities: DM and Echo

(hint: Dex and IVF)

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Key to Success

1. Start Slow (few select patients)
2. Select stable, low bulk, fit patients with good support
3. Start one patient at a time
4. Educate
   Educate
   Educate!
5. Plan for after hours
6. Make sure Tocilizumab is available! (Hint: Pharmacy)

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Nurse Symposium

Antibody Drug Conjugates

Bispecific Antibodies

Subcutaneous Immunotherapy

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Subcutaneous formulations

Approved agents:	Subcutaneous Use For:
• Methotrexate	Acute lymphoblastic leukemia
• Cladribine	Hairy cell leukemia
• Alemtuzumab	Chronic lymphocytic leukemia
• Trastuzumab	HER2-positive breast cancer
• Cytarabine	Acute myelogenous leukemia
• Azacitidine	Myelodysplastic syndromes
• Bortezomib	Myeloma; Mantle cell lymphoma
• Omacetaxine	Chronic myelogenous leukemia
• Bleomycin	Germ cell testicular cancer lymphomas
• Abagovomab	Ovarian cancer
• Daratumamab	Multiple myeloma and AL amyloidosis

Marzieh M, Mostafa K, Abolghasem A, Amir Hossein S, Arasteh O, et al. Subcutaneous Administration of Anticancer Agents: A Narrative Review. Case Rep Oncol Open Access. 2023; 2(1): 1006.

Efforts are underway to develop ICI subcutaneous formulations:

- *Atezolizumab*
- *Nivolumab*
- *Pembrolizumab*

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KEY UPDATE

CheckMate 67T

First presented at ASCO GU 2024

Subcutaneous nivolumab (NIVO SC) vs intravenous nivolumab (NIVO IV) in patients with previously treated advanced or metastatic clear cell renal cell carcinoma (ccRCC): Pharmacokinetics (PK), efficacy, and safety results from CheckMate 67T

May 6, 2024: the FDA accepted the Biologics License Application (BLA) for the subcutaneous formulation of Opdivo® (nivolumab) co-formulated with Halozyme's proprietary recombinant human hyaluronidase (rHuPH20) (herein referred to as " subcutaneous nivolumab") across all previously approved adult, solid tumor Opdivo indications as monotherapy, monotherapy maintenance following completion of Opdivo plus Yervoy (ipilimumab) combination therapy, or in combination with chemotherapy or cabozantinib.

The FDA assigned a Prescription Drug User Fee Act (PDUFA) goal date of **December 29, 2024**.

- First presentation of data evaluating subcutaneous nivolumab compared to its intravenous formulation
- A total of 495 pts were randomized to NIVO SC (n = 248) or NIVO IV (n = 247).
- The median age was 64/66 years in the SC/IV arms.
- Most pts were male. Average injection time with NIVO SC was < 5 minutes.

	NIVO SC	NIVO IV
C_{avgd28}, GMR (90% CI)[a]	2.098 (2.001–2.200)	
C_{minss}, GMR (90% CI)[a]	1.774 (1.633–1.927)	
ORR by BICR, % (95% CI)	24.2 (19.0–30.0)	18.2 (13.6–23.6)
ORR, relative risk ratio (95% CI)[b]	1.33 (0.94–1.87)	
Median progression-free survival by BICR, months (95% CI)	7.23 (5.13–7.49)	5.65 (5.29–7.39)
ADA-positive, n/N (%)	46/202 (22.8)	15/215 (7.0)
Safety (grade 3/4), n (%)	(N = 247)	(N = 245)
AE	87 (35.2)	100 (40.8)
Treatment-related AE	24 (9.7)	36 (14.7)
Serious AE	52 (21.1)	56 (22.9)
Treatment-related serious AE	16 (6.5)	16 (16.5)

The co-primary PK endpoints for noninferiority testing were time-averaged serum concentration over the first 28 days (Cavgd28) and minimum serum concentration at steady state (Cminss) determined by a population PK analysis. ADA: antidrug antibodies

Subcutaneous nivolumab demonstrated noninferiority efficacy to IV nivolumab and improved safety. If approved, SC nivolumab would represent the first subcutaneous PD-1 inhibitor approved in the USA

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KEY UPDATE

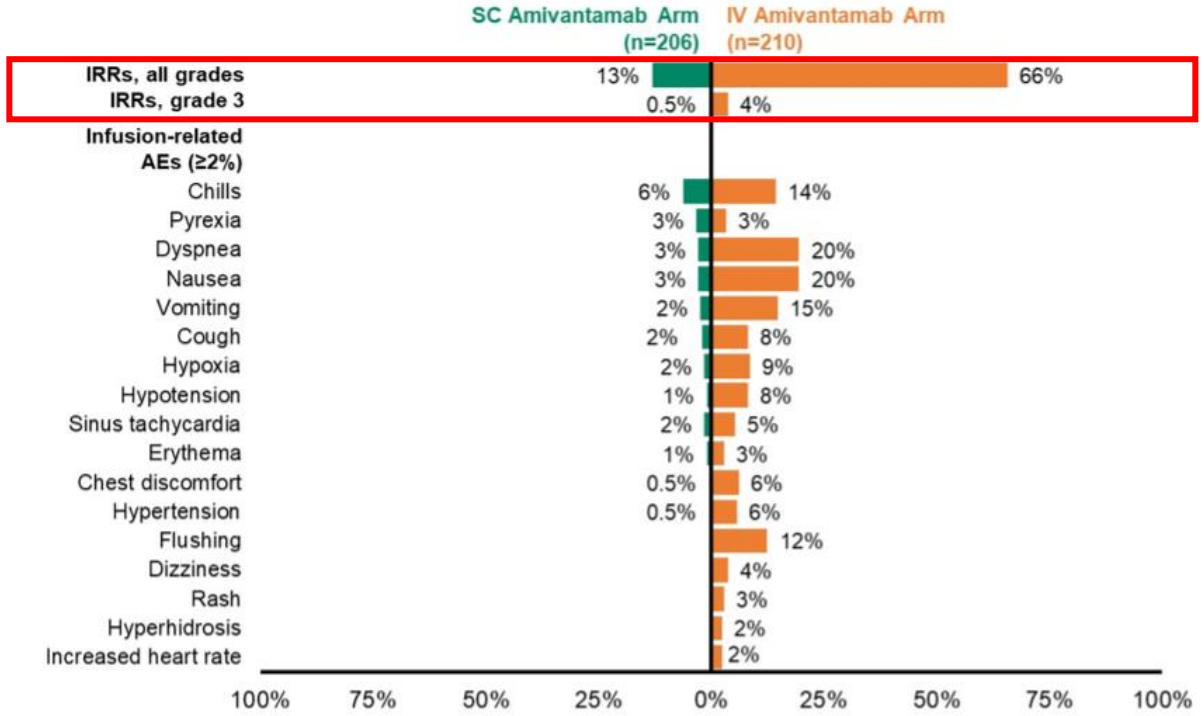
PALOMA-3

First presented at ASCO 2024

Subcutaneous Amivantamab vs intravenous amivantamab both in combination with Lazertinib, in refractory EGFR-mutated, advanced NSCLC: primary results, including overall survival from the global, phase 3, randomized controlled PALOMA-3 trial

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	**30 (24–37)**	**33 (26–39)**
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	**27 (21–33)**	**27 (21–33)**
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	**75 (69–81)**	**71 (64–77)**
Median time to response (range), mo	**1.5 (1.2–6.9)**	**1.5 (1.2–9.9)**

- First presentation of data evaluating subcutaneous amivantamab compared to its intravenous formulation
- A total of 418 pts were randomized to SC AMI + LAZ (n = 206) or IV AMI + LAZ (n = 212).
- The median age was 61/62 years in the SC/IV arms.
- Most pts were male; median prior lines of therapy was 2, and 34% of patients in each arm had a history of brain metastases
- Average injection time with SC amivantamab was < 5 minutes.



- AEs were consistent between arms, with a 5-fold reduction in infusion-related reactions

Subcutaneous amivantamab demonstrated noninferiority efficacy to IV amivantamab and improved safety. Yet to submit regulatory application seeking the approval of SC amivantamab in the USA

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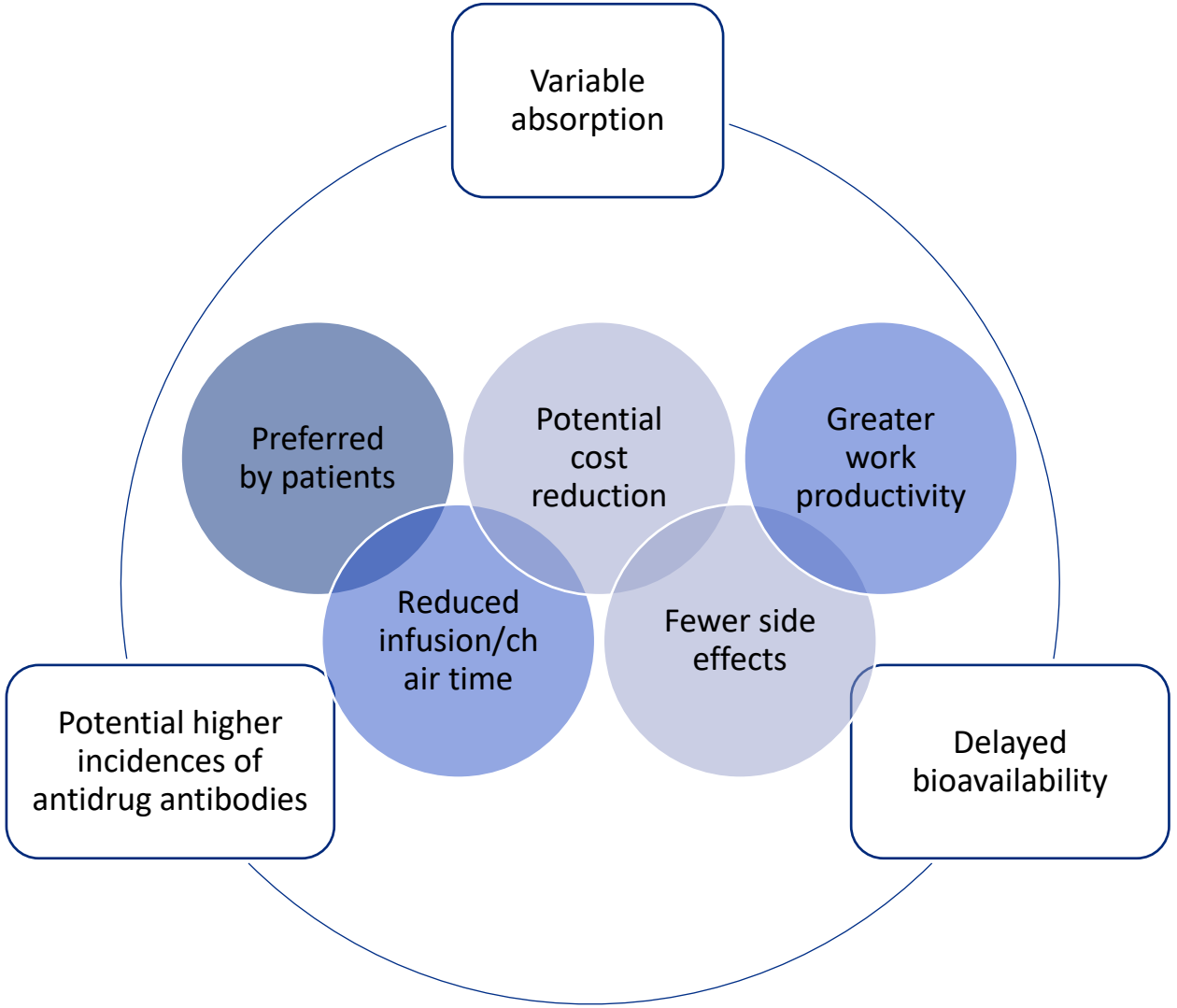
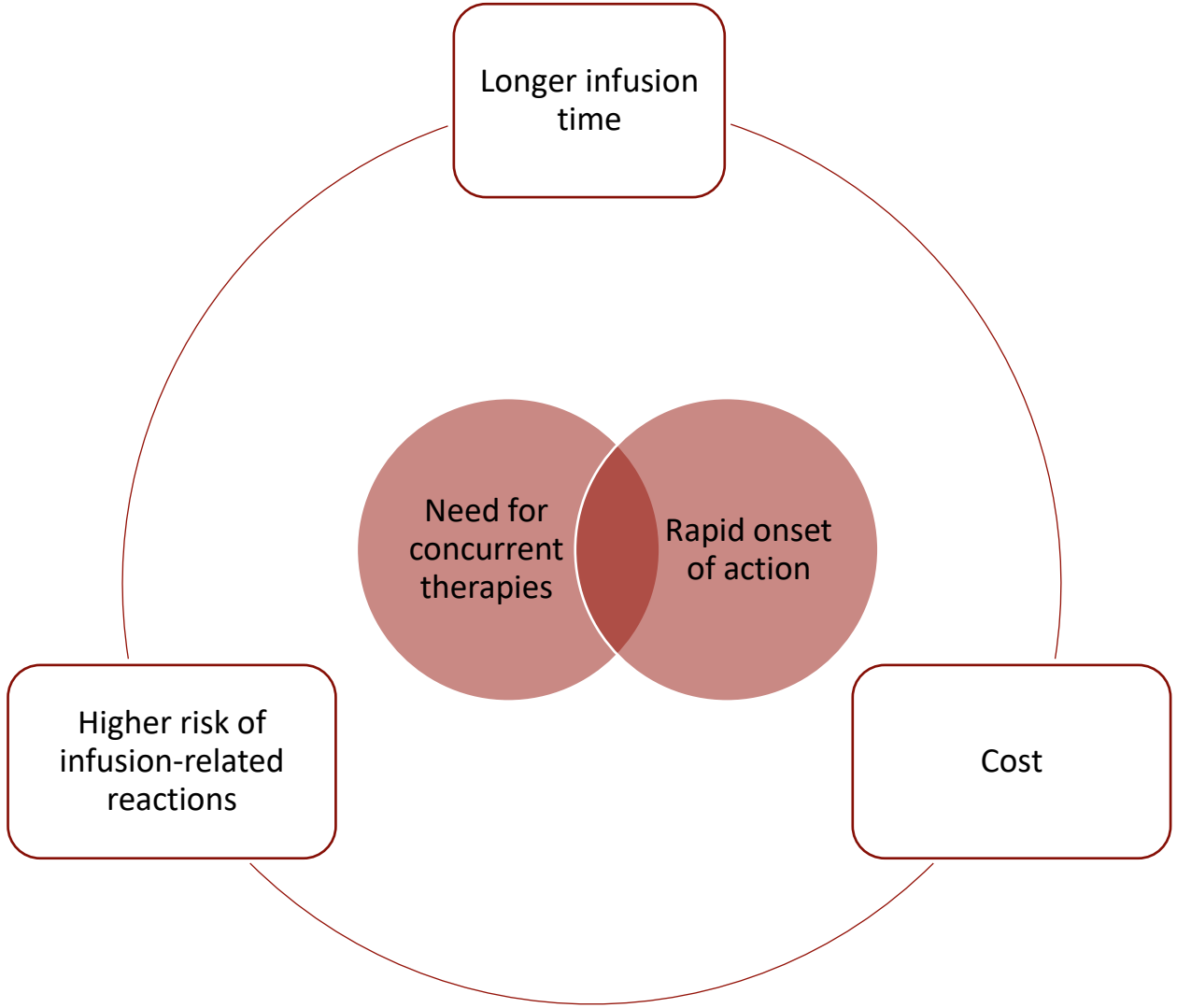
Subcutaneous formulations



IV formulations



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More to come…